Pharmacokinetics and Pharmacodynamic Clinical Protocol

For

PROTOCOL: NCT04037085

STUDY TITLE:

Ketamine to Improve Recovery After Cesarean Delivery – Part 1

(KINETIC)

VERSION WITH MODIFICATIONS APPROVED BY HUMAN SUBJECTS PROTECTION REVIEW BOARD (IRB) DATE: 4/28/2021

Brief Description

This is a drug study that will examine the physiochemical, PK/PD properties of ketamine infusion in postpartum lactating women and in women weaning from breastfeeding. Part 1 of this study will inform the safety of a future planned RCT studying the effect of ketamine vs. placebo administered during scheduled cesarean deliveries or in weaning women on pain, opioid use, side effects, breastfeeding, and other outcomes.

15 (goal of 6 complete subjects) mothers will be recruited who are planning to either exclusively bottle-feed or to withhold breastfeeding for the first 27 hours after birth (during infusion of 12 hours, plus 15 hours after infusion) or they will be women who have been breastfeeding and are planning on weaning their baby off of the breastmilk who will be at the CTRC clinic for 24 hours total. For the cesarean population, after cord clamping, an intravenous infusion of 0.1mg/kg/hr for 12 hours will be started without a loading dose. If the patient is a weaning woman, they will come into the CTRC clinic in Montefiore and will have infusion in the clinic for 12 hours. Side effects, vital signs, and pain/analgesia endpoints will be monitored and recorded. Breastmilk/colostrum, serum, and urine will be collected to measure ketamine and its metabolites. The results of part 1 will inform appropriate future trial in Part 2 (the Phase 2 RCT) to either exclude or permit breastfeeding mother-infant dyads.

Study Aims

The objective of this study is to assess pharmacokinetics of ketamine in the women immediately post cesarean delivery or women weaning from breastfeeding. Study Hypotheses: Breastmilk secretion of ketamine is low and poses minimal risk for neonatal exposure

Study Aims:
Aim 1. Evaluate breastmilk secretion of ketamine and its metabolites during and after administration of intravenous ketamine infusion in women immediately post C-section or women weaning from breastfeeding
Aim 2. Quantify pharmacokinetics of ketamine infusion in lactating people

Study Design

1. **Total number of subjects to be enrolled at this site:**
   15 (maximum)
2. **Describe and explain the study design:**
   Open-label lead-in evaluation of ketamine infusion and breastmilk secretion.

   Part 1 is an open-label evaluation in women who are either exclusively bottle-feeding, planning to withhold breastfeeding for the first 27 hours after birth, or weaning women. The goal is to get 6 complete patients (target n=6). Analysis of breastmilk for ketamine and metabolites will be done on each patient. The results of this part will inform conducting an additional future open-label evaluation in breastfeeding mother-infant dyads for ketamine and metabolites.

   The patients enrolled will undergo an open-label sub-anesthetic ketamine infusion at 0.1 mg/kg/hr to assess breastmilk secretion of ketamine and its metabolites. These women will be selected for their plan to exclusively bottle-feed or will be weaning; they will then receive the ketamine infusion in the trial dosing protocol, and provide blood and breastmilk samples during and after ketamine infusion, so that ketamine and its metabolites concentrations can be assessed.

Protocol for Study Drug/Intervention:
Ketamine - 0.1 mg/kg/hr IV infusion for 12 hours, not to exceed 8mg/hr.
Weight-based dosing will be done on term body weight (kg), minus 41% of ponderal increment (for the post-cesarean delivery cohort)

3. Describe the primary and secondary study endpoints:

Primary outcome: Breastmilk transfer: concentration of ketamine and its metabolites in breastmilk

4. List the inclusion criteria:

Cesarean Section Population:
Adult female patients (i.e., ≥18 years of age)
Able to provide informed consent
Cesarean Delivery, Scheduled or Non-Emergent (delivery within 15 minutes not necessary),
ASA PS 2 or 3, with or without E designation (delivery within 15 minutes not necessary)
Spinal anesthesia with intrathecal morphine
Multimodal postop analgesia with IV ketorolac, PO NSAID, and PO APAP
Women who do not plan to breastfeed or who want to temporarily withhold breastfeeding

Weaning Women Population:
Adult female patients (i.e., ≥18 years of age)
Able to provide informed consent
Female weaning baby off of breastfeeding
ASA PS 1, 2 or 3
Minimum production of 2mL/24 hours breast milk

5. List the exclusion criteria:

Cesarean Section Population:
Cesarean Delivery under General Anesthesia
Allergies to study medications
ASA PS 4 or 4E
ASA PS with E designation because delivery within 15 minutes required
ASA PS greater than 4 (moribund patients)
Contraindications to spinal anesthesia
Contraindications to NSAIDs (gastric bypass, etc.)
Contraindication to any other multimodal analgesia medicine
Psychiatric history (depression and anxiety NOT exclusion criteria)
Uncontrolled hyperthyroidism
Cardiac disease
Fever
Hypertension
Adverse occurrence during caesarean section such as hemorrhage, need for transfusion, hemodynamic instability
Placenta accreta or previa with large anticipated blood loss
History of hallucinations, alcohol or illicit substance use/abuse
History of chronic opioid therapy, or chronic pain (chronic pain - defined by any condition requiring consistent follow up with pain specialist or daily administration of pain medications that could augment sedative effects)
Pre-eclampsia with severe features

Weaning Women Population:
Allergies to study medications
ASA PS 4 or 4E
ASA PS greater than 4 (moribund patients)
Psychiatric history (depression and anxiety NOT exclusion criteria)
Uncontrolled hyperthyroidism
Cardiac disease
Fever
Hypertension
History of hallucinations, alcohol or illicit substance use/abuse
History of chronic opioid therapy, or chronic pain (chronic pain - defined by any condition requiring consistent follow up with pain specialist or daily administration of pain medications that could augment sedative effects)

Methods

1. **Provide a detailed description of all research activities**

PART 1: LACTATION STUDY
Women who are planning not to breastfeed, who are willing to withhold breastfeeding for the first 27 hours after delivery, or women who are weaning off of breastfeeding will be approached.

After electronic screening and confirming eligibility, approach will be by the clinical anesthesia team or by the bedside nurse to assess the patient's interest in hearing more about the study. Interested patients will be provided with a full explanation of study-related goals and procedures. The informed consent document will be reviewed in its entirety with the potential subject. All questions will be answered to the subjects' satisfaction. The patient may decide on participation in the study at any time during or after the initial encounter, and the desire and duration for a potential waiting period will be at the full discretion of the subject. The study coordinator or investigators can be contacted after the subject makes a volitional decision to participate in the study. The physician investigators will obtain written informed consent. The consent will be provided by the patient themselves; no patients will be approached or recruited if they are unable to consent for themselves. Subjects will not be informed of the outcome of the study at this time except through routine reporting structures available to the public forum via ClinicalTrials.gov.

OR Women who are weaning from breastfeeding. We will use multiple recruitment methods which are shown in the recruitment section. The women will come into the CTRC in Montefiore to provide consent. Interested patients will be provided with a full explanation of study-related goals and procedures. The informed consent document will be reviewed in its entirety with the potential subject. All questions will be answered to the subjects' satisfaction. The patient may decide on participation in the study at any time during or after the initial encounter. The study coordinator or investigators can be contacted after the subject makes a volitional decision to participate in the study. The physician investigators will obtain written informed consent. The consent will be provided by the patient themselves; no patients will be approached or recruited if they are unable to consent for themselves. A study physician will perform a history and physical and confirm ASA inclusion criteria after consent on day of study drug administration. For this weaning population, a urine pregnancy test will be performed the morning of CTRC visit, after informed consent and prior to any study related procedures. A positive test allows

the PI or CO-Is to re-evaluate the participants eligibility for this study. Subjects will not be informed of the outcome of the study at this time except through routine reporting structures available to the public forum via ClinicalTrials.gov. The CTRC has 24/7 RN staff and it will be a 1:1 participant:RN ratio. All staff are trained on IV ketamine protocol. They will be discharged after 24 hours after the start of infusion or as seen medically fit by the discharging physician.

Ketamine will be delivered in an open-label fashion as follows: 0.1mg/kg/hr IV infusion after cord clamping or at CTRC at a scheduled time with the participant and clinic (maximum allowable dose 8mg/hr infusion rate), for a total duration of 12 hours. Pharmacokinetic studies will be performed on breastmilk, serum, and urine samples.

Blood samples: 3mL whole blood at each sample from an indwelling intravenous catheter or by fresh sample by 25g or smaller butterfly needle. Specimens will be placed on ice and stored within 24 hours at -20 to -80C until analysis. Timepoints for collection: 8-10hrs into study drug infusion; 12hrs into study drug infusion; after infusion end at the following times: 0.5hrs, 1hr, 2hr, 4hr, 8hr, 24hr.

Urine: Total volume of maternal urine will be taken in the first 24 hours post-operatively. Collected in hat placed in toilet bowl and filled into a urine container. Samples can be stored/stable at room temperature and transported to the laboratory for analysis within 24 hours.

Breastmilk: colostrum/breastmilk samples will be expressed by hand expression or pump to get total volume into "snappies (R)" specimen collection devices. Specimens will be placed on ice and stored within 24 hours at -20 to -80C until analysis. Timepoints for collection: T0-2hrs after infusion start (at first opportunity), during infusion (4hrs, 8hrs, 12hrs), after infusion ends (2hrs, 4hrs, 8hrs, 24hrs). Per study team communication, the post c-section and weaning samples will undergo the same analysis for assessment of metabolites, confirmed by Co-I, Dr Venkataraman, overseeing the analysis.

Pain assessments: During 72 hour hospital stay, medical records will be reviewed to collect pain scores during the hospital stay

Side effect electronic diary: a novel app has been developed for the purpose of this study to make sound alerts to collect data at appropriate times. Assessments will be made within 1hr after start of study drug (at the earliest possible time); every 4 hr thereafter until 12 hr after study drug infusion start. Assessments will include: Dizziness, lightheadedness, bad dreams, nausea, vomiting, itchiness, hallucinations; LSD short form of Addiction Research Center Inventory, ARCI (psychomimetic effects).

Maternal vital signs (blood pressure, pulse rate, temperature, heart rate, respirations, and oxygen saturation, Richmond agitation-sedation scale (RASS) score) will be measured after infusion start: every 30 min for one hour, then q1hr for 3 hours, then every 4 hours per existing clinical standards for the 12-hour duration of infusion (existing clinical standards: blood pressure, pulse rate, temperature, heart rate, respirations, and oxygen saturation). If the infusion rate is increased by the anesthesiologist investigators, then vitals are rechecked within one hour. When the infusion is discontinued at 12 hours, vital signs monitoring will be hourly for the first 4 hours, then every 4 hours including blood pressure, pulse rate, temperature, heart rate, respirations, and oxygen saturations, until 24 hours after the start of the study drug infusion (= 12 hours after study drug discontinuation)