

Ketamine Lactation Protocol

Date: December 19, 2019

Title: *The Pharmacokinetics of Ketamine in the Breast Milk of Lactating Women: Quantification of Ketamine and Metabolites*

ClinicalTrials.gov ID: NCT04285684

Sponsor: The Ketamine Research Foundation

Clinical Coordinator: Phil Wolfson MD,

Principle Investigators: Rob Cole MD, Melissa Whippo,

LCSW

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Title: *The Pharmacodynamics of Ketamine in the Breast Milk of Lactating Women: Quantification Over 3 Half-Life Intervals of 3 Hours Each*

Protocol: PP1

Purpose: There is no available data on presence and concentration of ketamine in breastmilk. There are statements in the literature made as to the safety of the use of ketamine in lactating women, though these are unsupported. This information is pertinent for the treatment of women who are lactating who may have depression, PTSD, postpartum depression, and other emotional difficulties and would benefit from ketamine treatment. The objective of this study is to... o measure the presence and concentration of ketamine in breastmilk

Background

Ketamine was developed as an anesthetic agent, by Parke Davis, in the search for analogs resulting from recognition of the anesthetic properties of phencyclidine, the first drug developed in the arylcyclohexylamine structure during the late 1950s, 1960s. This drug was marketed as Sernyl and in addition to anesthesia, was also noted to cause significant increase in blood pressure and often prolonged postsurgical emergence delirium, even to the point of unmanageable, and at times, violent, 'manic behavior'. Ketamine was developed clinically in the mid 1960s and was a successful anesthetic agent with fewer adverse effects than the parent compound. It was dubbed a 'dissociative anesthetic' by the wife of Edward Domino, the primary research clinician, as a solution to the descriptive puzzle offered by the drug's novel effects. Ketalar, ketamine's brand name, was approved by the FDA in 1970 for use in children, adults, the elderly and animals as an anesthetic agent. During the Vietnam War, ketamine became widely used as a field anesthetic administered to wounded soldiers because of its fast onset and quick recovery period and its property of maintaining or elevating blood pressure in trauma situations.

Ketamine's potential to treat different psychological or psychiatric problems commenced in 1974 in Argentina as an adjunct for antidepressant psychotherapy (Fontana 1974). In Mexico, the psychiatrist Salvador Roquet introduced ketamine to patients in group settings as a component of his approach to psychedelic psychotherapy (Kolp et al., 2007). And then he brought ketamine to the attention of investigators at the Maryland Psychiatric Research Center, Stan Grof and Bill Richards among them. Ketamine's versatility extends to analgesia and, for example, was used to treat patients who were at the scene of the 2005 London underground bombings. Following this awful act of terrorism, paramedics in the UK were authorized to possess and administer ketamine for pain relief.

Ketamine is currently listed as one of the two injectable medicines under general anesthetics in the WHO Model List of Essential Medicines. The Model List designates medications determined "satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in the appropriate dosage forms, and at a price that individuals and the community can afford" (WHO Technical Report Series 2000).

Pharmacology

Ketamine is available in two enantiomers: the S (+) and the R (-) configurations. Most pharmacological preparations include an equimolar racemic mixture of the two enantiomers.

Although racemic ketamine has the broadest worldwide use, S(+)-ketamine is available in some European countries like Denmark, Finland, Germany and the Netherlands and will come to market as a patented nasal preparation for psychiatric use in late 2018.

Ketamine's putative action is as an N-methyl-D-aspartic acid (NMDA) glutamate receptor antagonist. Multiple routes of administration are utilized by practitioners treating depression and other psychiatric conditions, each with its own unique pharmacokinetics, have been investigated in the treatment of depression, including intravenous, intramuscular, intranasal, sublingual, anal, and oral delivery. Ketamine's antidepressant activity is believed to stem from its antagonism of NMDA receptors, which are widely expressed in the brain. When NMDA receptors on gamma-aminobutyric acid (GABA)-ergic neurons are antagonized, downstream glutamatergic neurons are disinhibited. This increased glutamatergic activity impacts neural signaling, synaptic plasticity, and connectivity. It is posited based on animal models that ketamine-induced synaptic potentiation and proliferation may play a key role in eliciting antidepressant effects. Ketamine also impacts other neurotransmitter systems, affecting cholinergic, opioidergic, monoaminergic, and GABAergic function.

The bioavailability of Intramuscular ketamine is similar (93 -95%) to IV ketamine (Clements et al, 1982). Intranasal ketamine has been used in anesthesia and found to have a favorable pharmacokinetic and pharmacodynamic profile relative to oral and rectal administration (Costantino et al, 2007). In a blinded, randomized, controlled trial of 20 MDD patients, 50 mg of intranasal ketamine was found to elicit only mild side effects and produced significant antidepressant activity within 24 hours of administration (Lapidus et al, 2014). Estimates of intranasal absorption are variable ranging from 30-50%, with the lower figure seeming more the case in clinical practice. In several studies, Sublingual and Oral ketamine have a calculated bioavailability of about 30 % and 20 %, respectively (Lara et al, 2013; Paslakis et al, 2010). Again, in clinical practice, these percentages appear to be lower—20-30% for sublingual preparations and perhaps 10% for the oral administration. Of 27 patients with MDD given variable, escalating doses of sublingual ketamine, 20 experienced antidepressant efficacy (Lara et al, 2013). A retrospective review of 20 hospice patients receiving a single 0.5mg/dose of ketamine, given orally for 22 found significant antidepressant efficacy (Iglewicz, 2015).

Ketamine is water and lipid soluble. It is absorbable by IV, intramuscular, intranasal, subcutaneous, epidural, oral, and rectal routes of administration. Differences in the effects of ketamine are entirely determined by the degree and rapidity of absorption. Ketamine's relatively low binding capacity to plasma proteins leads to rapid brain uptake and distribution (Weber et al. 2004). The differences in bioavailability are due to gastrointestinal absorption and first-pass metabolism. The α -elimination phase half-life is only 11 minutes, while the β -elimination phase is about 2.5 hours (Wieber et al., 1975).

Ketamine undergoes extensive hepatic metabolism. It is N-demethylated by cytochrome P450 enzymes in liver microsomes into NK and other metabolites (Hijazi and Boulieu 2002). The principal isoform responsible for demethylation is CYP3A4, with minor contributions by CYP2B6 and CYP2C9 (Hijazi and Boulieu 2002). NK plasma levels are about three times higher after oral administration than after IV administration. The metabolites of nor-ketamine primarily undergo renal excretion; about 91 % of ketamine is excreted in the urine as metabolites, and 1–3 % is found in the feces (Chang and Glazko 1974). Parenteral ketamine (as hydrochloride) is rapidly distributed throughout the body into widely perfused tissues, including the brain. It is likely

excreted into breast milk and does cross the placenta. However, it was posited to have no clinically relevant or adverse effects on neonates (Little et al., 1972). As this was early work and related to anesthesia, this remains an open issue for often repeated psychiatric use by pregnant or lactating mothers.

Ketamine's tolerability and safety have been demonstrated over almost 5 decades. It has been used as an anesthetic for adults and children since the 1960s and has been used in neuropsychiatric research for more than two decades. Anesthetic doses from 1 to 3 mg/kg are considered to be very safe (Wan et al. 2015). Subanesthetic doses of ketamine (from 0.1 to 2 mg/kg) have been associated with transient side effects including neurocognitive, sensory-motor, and hemodynamic changes. A pooled data study from three different clinical trials of subanesthetic IV ketamine administration in MDD patients found that adverse effects common within the first four hours of administration included dizziness, derealization, and drowsiness. Whether these are truly to be considered 'adverse' or are part and parcel of ketamine's actual effects that result in the antidepressant and/or therapeutic benefits is the subject of much debate. One third of all patients experienced transient hemodynamic changes, particularly elevated blood pressure. There have been no cases of persistent neuropsychiatric sequelae, medical effects, or increased substance abuse in clinical practice. Route of administration and dose provided will also affect tolerability. While there have been multiple reports of dissociative and psychotomimetic effects of ketamine with IV and IM preparations, a trial of sublingual ketamine in 27 MDD patients reported no such side effects (Lara et al., 2013). A trial of intranasal ketamine also found only small increases in dissociative symptoms (Lapidus et al., 2014).

A cautionary here in that increasing dosages of ketamine through any route of administration will result in an increase in dissociative effects.

Ketamine has been approved by regulatory bodies worldwide for use as an anesthetic and an analgesic in both human and veterinary medicine. Ketamine was classified in 1999 as a Schedule 3 substance. Off label use has been a constant in ketamine's history.

Summary of Research Design: This study will be conducted with 4 lactating women who agree to postpone breastfeeding and provide samples of their milk. Ketamine's half-life is variously placed at 2 and a half to 3 hours. The most reliable data puts ketamine's half-life

at 2.1 hours and for the metabolite—norketamine at 1.2 hours—this from a ketamine study in children indicating the safety of this medicine (Herd et al 2002). Samples will be collected prior to injection for baseline measurement, and timed at 3, 6, and 9 hour intervals--choosing the maximum half-life duration. Two dosages will be administered: 0.5ml/kg and 1.0ml/kg. administered Intramuscularly (IM). Each administration will be separated by a minimum of 3 days and preferably one week.

The study subjects participants to greater than minimal risk because the protocol design calls for administration of IM ketamine. While the safety of IM ketamine administration is well established over decades of use, participants will be provided with full information on risks.

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The IM route confers rapid onset—2-5 minutes for effect and a reliable approximate 95% absorption of ketamine. The dosage range for a 50 kg woman amounts to 25-50mg and for a 70kg woman 35mg-70mg, both quantities well within commonly used therapeutic administration of IM ketamine for depression and other psychiatric diagnoses (Dore et al, 2019).

While psychiatric use of ketamine may well exceed 1.0 mg/kg, blood concentrations of ketamine for anesthetic use have tended to follow a linear pattern of concentration, enabling estimates of concentration in breast milk, should there be a decision to exceed 1.0mg /kg IM in clinical practice.

Inclusion Criteria

Obtained by Interview/Self-Report

- • Age 21-45
- • Postpartum with established lactation for a minimum of 3 months.
- • Ability to pump breast milk and to provide a reservoir for infant feeding prior to the study; or acceptance of bottle feeding by the infant.
- • In good health—normal BP/P; afebrile-temp ascertained; review of systems by MD; absence of diagnosed illnesses.
- • Not pregnant--Pregnancy tested for before each administration by urine assay.

Exclusion Criteria:

- • Hypertension with a BP greater than 145/90
- • Subjects must be offAbsence of all psychiatric medications specifically; medications and supplements, or evaluated by the PI for non-interference
- • No alcohol or other substances such as marijuana for 72 hours or more.
- • Weight <50kg or > 90kg.
- • Pregnancy

Method of Subject Identification and Recruitment

Two of the investigators have close connections to practicing OB/GYNs, one being one of these himself; and the other has a practice with postpartum women in part at a local university medical school. As only 4 subjects will take part, with the possibility of drop-out

requiring further recruitment this 'n' is compatible with the outreach potential of the Investigators. Lactating patients and staff in both situations will be approached for an initial screening conversation.

No advertising is involved.

Procedures

Initial screening for participation will be conducted by an investigator, via telephone.

The IC and Intake form will be emailed/mailed to a potential participant based on the suitability for admission to the study as per the screening determination. The intake form assesses current and previous illnesses, psychiatric conditions, medications, supplements and emergency contacts, etc.

Review of the Intake form will occur prior to the formal Intake Interview to be performed at the site. This review will again determine potential eligibility.

The intake Interview at the site will take place with two investigators present and will take as long as necessary to review the protocol, the IC, the information on the actual Intake form, and to determine admission to the study. This will enable Investigators to screen potential subjects prior to enrollment—as is our general practice. The Informed Consent will be provided along with the Intake Form for review by the subjects prior to making a decision to proceed with the study intake process. Subjects will discuss, and make a decision to sign, or not, the Informed Consent.

HIPAA confidentiality will be maintained throughout. Subjects will be given a numerical designation for all materials, other than the written forms discussed herein. All written and confidential materials will be stored in a locked file on premises available only to the Investigators.

Preliminary lab tests, BP and PR and an initial pregnancy test will be performed.

BP and PR will be performed at 1 hour post-administration to assess peak impact on cardiovascular status.

This study will assess if the rapid elimination of ketamine facilitates a short and tolerable suspension of breastfeeding. If the study determines that significant amounts of ketamine remain in breast milk after 9 hours and 3 intervals, a decision will be made to add further intervals for assessment. The collection at 3 hour intervals will continue until ketamine levels are undetectable.

No hazardous substances or procedures are involved

Pumping of breast milk will be performed by the subjects, collected, and preserved as per the lab's criteria. Every attempt will be made to collect milk in volume. The study will provide a pump for collection to each participant

Subjects may stay at the clinic for the duration of the collection , or may be provided with instructions and collection materials for at home pumping if the duration is prolonged beyond 9 hours. As much as possible, tThe samples will be collected by the next day.

Subjects will refrain from eating and drinking 3-4 hours before receiving ketamine, this to prevent stomach contents that may contribute to nausea, and reduce any risk of aspiration. Subjects are permitted one cup of coffee if they are caffeine dependent, or juice or water at 3-4 hours prior. Subjects will provide consent for fasting prior to its initiation verbally and later fully in person at the clinic.

A urine pregnancy test will be conducted prior to each administration of ketamine.

A first subject in the study will have milk collected at 0, 3, 6, 9, 12 and 15 hours to determine if these intervals are sufficient to characterize a basic pharmacodynamic profile. If there is a negligible quantity in the samples as the time frame proceeds, the lab will not analyze subsequent samples. Once determined, the study will proceed with the remaining 3 subjects at the intervals projected from the first subject

Two dosages will be administered: 0.5ml/kg and 1.0ml/kg. Intramuscularly (IM). Each administration will be separated by a minimum of 3 days and preferably one week. Each session will follow the same process and procedure as described herein and occur at the study site.

PROCEDURE TIMING CHART

<u>HOUR</u>	<u>PROCEDURE</u>
-30 minutes	Arrives at Study Site Pregnancy Test Review of IC and Fasting with Consent
-!5	BP, HR, Review of Systems
0 Hour	Zero Time Pump
15	IM 0.5mg/kg; or Second Session 1.0mg/kg
15-60	Support for Subject who is reclining on sofa with eyeshades and ambient music

1 hour	BP, HR
1-3 hours	Support for subject and integration of experience
3 hours	BP, HR, Second Pump
3-6 hours	Subject relaxing at Study Site
6 hours	Third Pump
9 hours	Fourth Pump
12 hours	Fifth Pump if necessary (as per procedure)
Home	Milk has been quantified for volume at each pump and an aliquot labelled, saved and refrigerated. If subject has gone home earlier—at 6 hours or later, subject will be contacted to pump at the assigned intervals and an aliquot refrigerated for pickup and delivery to the clinical lab for analysis.

Safety: Administration of ketamine will occur in office premises and with standard of care safety equipment available. This includes CPR trained personnel, ambu bag, defibrillator and a suction device. MDs will be present on site throughout and will administer the injections.

Injections are provided with a 25 gauge, 1 inch needle using ketamine in a sterile 100mg/ml concentration. Total volume of ketamine fluid will be less than 1 cc. Occasionally, there may be a slight bleed from the injection site. There may be mild ache at the injection site for up to a few hours. Injections are intra-muscular and into the deltoid or buttocks regions.

Subjects will be provided in advance for preliminary screening with our standard intake form to assess current and previous illnesses, psychiatric conditions, and emergency contacts, etc. This will enable Investigators to screen potential subjects prior to enrollment—as is our general practice. The Informed Consent will be provided along with the Intake Form for review by the subjects prior to making a decision to proceed with the study intake process.

At Intake, subjects will discuss, and make a decision to sign, or , the Informed Consent.

HIPAA confidentiality will be maintained throughout. Subjects will be given a numerical designation for all materials, other than the written forms discussed herein. All written and confidential materials will be stored in a locked file on premises available only to the Investigators.

No hazardous substances or procedures are involved

Methods

Quantitative analysis of ketamine will be performed by Alan Wu PhD, Professor of Laboratory Medicine at UCSF School of Medicine and Kara Lynch at UCSF.

- 1) Lab will prepare a standard for analysis of ketamine and its principle metabolite norketamine in breast milk. The half-life of ketamine is 2.1 hours, and that of norketamine 1.2 hours (Herd et al 2007). The study will view the half-life as being a conservative 3 hours.

Subjects will refrain from eating and drinking 3-4 hours before receiving ketamine, this to

prevent stomach contents that may contribute to nausea, and reduce any risk of aspiration. Subjects are permitted one cup of coffee, juice or water at 3-4 hours prior if they are caffeine dependent. PROVIDED IN LAST VERSION

- 1) A urine pregnancy test will be conducted prior to each administration of ketamine.
- 1)
- 2) A first subject in the study will have milk collected at 0, 3, 6, 9, 12 and 15 hours to determine if these intervals are sufficient to characterize a basic pharmacodynamic profile. If there is a negligible quantity in the samples as the time frame proceeds, the lab will not analyze subsequent samples. Once determined, the study will proceed with the remaining 3 subjects at the intervals projected from the first subject. The lab will process the samples from the first subject as rapidly as possible to enable continuation of the study. Breast milk will be collected until ketamine levels are undetectable. If significant amounts of ketamine are found in samples from the 3 subsequent subjects at the last interval determined by the profile of the first subject, additional time frames for collection will be added. If necessary, the process will be repeated to fully document pharmacokinetics.

As real time testing of ketamine content in breastmilk is not possible, the first subject will be the exemplar for the timing of the resumption of breast feeding based on the data obtained, such as not detectable at 9 hours, hence breast feeding may resume. For that first subject, breast feeding may resume at 18 hours, which corresponds to 9 half-lives for ketamine, 4 half-lives being the accepted timing for the absence of a molecule. This will be confirmed by lab testing as quickly as possible for the first subject.

- 3) Pumping of breast milk will be for a full expression so as not to influence concentrations in subsequent sampling intervals. The volume of breast milk will be quantified for each expression.
- 4) Milk will be refrigerated in sterile containers and aliquots of one ounce will be brought to the lab refrigerated as soon as possible. A second aliquot of each

expression will be frozen in the event of loss or spoilage of the first aliquots, site to be determined.

1. 5) Each aliquot will be labelled with coded subject designation, concentration of ketamine administered, date, and interval. The lab will be provided with the actual quantity of ketamine administered to each subject at the 0.5 and 1.0mg/kg levels and the weight of each patient in kgs.
 - 1)
1. 6) The Lab will provide the data to KRF in formats suitable for journal publication.

INTAKE FORM ATTACHED

AS PREVIOUSLY INDICATED THERE ARE NO QUESTIONNAIRES BEING ADMINISTERED— THIS WAS DELETED FROM THE PRIOR REVISION

Inclusion Criteria

- Age 21-45
- Postpartum with established lactation for a minimum of 3 months.
- Ability to pump breast milk and to provide a reservoir for infant feeding prior to the study; or acceptance of bottle feeding by the infant.
- In good health—normal BP/P; afebrile-temp ascertained; review of systems by MD; absence of diagnosed illnesses.
- Not pregnant--Pregnancy tested for before each administration by urine assay.

Exclusion Criteria:

- Hypertension with a BP greater than 145/90
- Absence of all psychiatric medications specifically; medications and supplements, or evaluated by the PI for non-interference
- No alcohol or other substances such as marijuana for 72 hours or more.
- Weight <50kg or > 90kg.
- Pregnancy

Potential Adverse Effects

- • Nausea and vomiting—a less than 5% incidence of intolerability to ketamine.
- • Transient hypertension—BP will be monitored. In clinical practice, and in this age group, this has not occurred with any frequency.
- • Ketamine is a dissociative anesthetic and subjects have a high likelihood of experiencing dissociative effects during the first two hours following ketamine's administration. Generally, the major impact occurs in the first hour, with full recovery to baseline by 3 hours. The Investigators have conducted thousands of sessions in which dissociative effects are part of the ketamine assisted

psychotherapy (KAP) approach, including at much higher doses than those being administered in this study. Subjects may experience, an altered mental state in which there is an imaginative stream of associations, sensations and imagery. There can be anxiety accompanying a shift from ordinary reality. The Investigators have specialized in developing a transformative psychotherapy with utilization of this state and are fully equipped and experienced in dealing effectively with this state. Subjects will be prepared for the possibility of this

- experience. Administration will be conducted in the same comfortable setting in which KAP sessions are routinely provided. Investigators are continually present throughout the time frame of this experience, however long it may persist. Subjects will remain in the office until fully recovered and will have a ride home and will not drive themselves.

- • Agitation—may occur transiently with dissociative effects. Subjects will remain in the clinical setting until ketamine’s influence has passed and they are safe to leave. We have never had to treat agitation, as it passes, and reassurance and support have been sufficient to enable attainment of calmness. In the event of unusual agitation that is a risk to the patient, sublingual lorazepam can be administered. With over 500 patients and several thousand ketamine sessions, this has never occurred.
- • Safety in operating machinery and driving—Subjects will have rides home when ready to leave.
- • No long term negative effects involving administration of ketamine in these dosages and frequencies have been reported in vast numbers over many decades of use.

A follow-up formal telephone session will occur at 4 weeks after the second administration. Questions will focus on any adverse effects on subjects or infants, difficulties in resuming breast feeding, psychological difficulties and insights not discussed in the prior 4 weeks of follow-up availability. Throughout the study, subjects will be reachable by their cell phones for emergency and consultative contact with the Investigators—who will have developed an on-call schedule.

Potential Benefits to Subjects

Ketamine administered in this clinical environment may well contribute to a sense of well-being and an exploration of consciousness. If emotional issues arise these will be fully processed. The Study Staff are skilled psychotherapists, versed in the practice of ketamine assisted psychotherapy.

Subjects may well feel they are contributing to the benefit of women who have postpartum symptoms and disorders.

Method of Subject Identification and Recruitment

Two of the investigators have close connections to practicing OB/GYNs, one being one of these himself; and the other has a practice with postpartum women in part at a local

university medical school. As only 4 subjects will take part, with the possibility of drop-out requiring further recruitment this 'n' is compatible with the outreach potential of the Investigators.

No advertising is involved.

Screening Script: *The Ketamine Research Foundation is conducting a study of the presence and concentration of ketamine in breast milk following two administrations of ketamine by injection intramuscularly. This study is in preparation for use of ketamine as an assisted psychotherapy for women suffering with postpartum depression. If you agree to participate, ketamine will be*

administered to you on two separate occasions based on your body weight. You would spend at least 10 hours at our comfortable offices in San Anselmo under the supervision of MDs and psychotherapists. You would need to pump breast milk on at least 3- 4 occasions at 3 hour intervals. You will be asked to fast for 3-4 hours prior to administration of ketamine to reduce the possibility of nausea which may occur and does occur in a small percentage of patients who receive ketamine. The effects of ketamine may would last for up to 2 hours, one hour of which can be expected to be a significant altered state and you would be lying down for the experience. Payment for participation includes cost of transportation and an initial stipend on acceptance into the study of \$100, and on completion a second \$100 stipend. Ketamine is known for its safety and positive effects on depression and other emotional difficulties. This is not about psychotherapy, but you will receive full attention for any emotional experiences you may encounter. You will be able to have a person of support present and your child as well. You will not be able to breast feed during the study session. To qualify, you need to be in good health, between the ages of 21 and 45, have been lactating for at least 3 months, not be on medication, and have normal blood pressure.

To be interviewed for the study, please email to ketamine.research@gmail.com.

Thanks for your consideration!

Phil Wolfson MD—Director

Informed Consent

All study subjects will have full capacity to consent. The Informed Consent will be mailed to subjects for their review prior to enrollment. The IC will be presented to subjects by the staff, reviewed for subjects understanding of the IC and what is involved in the study, for discussion and questions and clarification. Subjects may elect to withdraw from the study prior to receiving the first and second injections—without consequence. The IC is attached.

Study subjects will be fully aware that they will not breast feed infants for the period of the study so as not to expose infants to ketamine in breast milk.

Costs to the Subject and Reimbursement for Participation

Subjects will not bear any costs and will be reimbursed for travel expenses to the Study Site. Subjects will receive a stipend of \$200 for participation--\$100 paid on enrollment and \$100 paid at conclusion of the second event.

Data Analysis

As data is accumulated by the laboratory, it will be presented as both absolute quantities and graphed. Subject data will be correlated with concentration in breast milk

according to age, body weight, dosage, volume of milk collected, length of breast feeding to the time of the study—months.

Data Storage and Confidentiality

Data will be inputted at the site into an Excel digital format with a matrix with subjects as specified above. No identifying data will be inputted and the study will be fully HIPPA compliant. Subjects will be coded as follows: 1A, 2B, 3C, 4D, and so on if more than 4 subjects are included in the Study. Access to this data will be restricted to Investigators and stored on a limited access backup disc. ADDED Written materials will be stored at the study site in a locked file cabinet, with access controlled by the Clinical Coordinator.

Potential Treatment for a Research Related Injury

Should a research related injury occur, subjects will have full support of the Investigators for treatment based in depth, frequency and duration on the nature of that injury. Subjects have full access to the investigators by phone and email and will be contacted in follow-up directly at 4 weeks after the last ketamine session.

The study will secure insurance specific to the possibilities arising to subjects as a result of their participation in the study--which will include medical coverage.

The IC includes language pertinent to arbitration should that be necessary to determine the responsibility of the study for an injury should it occur and there be a dispute.

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Appendix A

1. Treatment Options

- 2. [Anesthesia](#)
- 3. [Ketamine](#)
- 4. Breastfeeding Warnings
[Print Share](#)

Ketamine Levels and Effects while Breastfeeding

Summary of Use during Lactation

Breastmilk levels of ketamine have not been measured after administration to humans. Minimal data indicated that ketamine use in nursing mothers may not affect the breastfed infant or lactation. Until more data are available, ketamine

should only be used with careful monitoring during breastfeeding.

Alternate agents are preferred.

Drug Levels

Maternal Levels. Relevant published information was not found as of the revision date.

Infant Levels. Relevant published information was not found as of the revision date.

Effects in Breastfed Infants

Four mothers who received epidural analgesia with lidocaine and bupivacaine for cesarean section also received general anesthesia with ketamine and midazolam (dosages not specified). Their infants were either breastfed or received their mother's breastmilk by bottle. No adverse effects were reported in the infants.[1]

Effects on Lactation and Breastmilk

A pregnant woman sustained 28% body surface area burns near term. She underwent an emergency cesarean section on her due date under ketamine anesthesia. Although the infant required vigorous resuscitation, the infant began

breastfeeding immediately. The infant had transient jaundice that resolved in a few days.[2]

A study compared women undergoing cesarean section who received either placebo or S-ketamine (esketamine) 0.5 mg/kg intramuscularly, followed by a continuous infusion of 2 mcg/kg/minute for 12 hours. This low dose was used to enhance analgesia and reduce residual pain rather than to provide anesthesia. All women received intraspinal bupivacaine 8 to 10 mg and sufentanil 5 mcg for analgesia, as well as midazolam 0.02 mg/kg intravenously before the S-ketamine or placebo injection. Postoperatively, patients received patient-controlled intravenous morphine for 24 hours, followed by acetaminophen, oral ketorolac and a single dose of ondansetron 8 mg intravenously as needed. Of the 56 patients enrolled in the study (28 in each group), 13 in each group were contacted at 3 years postpartum. Patients who received placebo reported breastfeeding for an average of 10.5 months and those who received S-ketamine

reported breastfeeding for an average of 8 months; however, the difference was not statistically significant.[3]

A randomized, double-blind study compared the effects of intravenous propofol 0.25 mg/kg, ketamine 0.25 mg/kg, ketamine 25 mg plus propofol 25 mg, and saline placebo for pain control in mothers post-cesarean section. A single dose was given immediately after clamping of the umbilical cord. The time to the first breastfeeding was 58 minutes in those who received placebo, 31.9 minutes with

ketamine and 25.8 minutes with propofol plus ketamine. The time was significantly shorter than the other groups with the combination.[4]

APPENDIX B—INTAKE FORM

DATE:

The Ketamine Research Foundation
STUDY INTAKE FORM

Confidential Client Information

Welcome to our Study.
Please fill out the following as completely as possible.
This information is confidential.

- 1.
Name:

- 2. Address:
Street/PO box

- 3. City: State:
Zip/Postal Code:

- 4. Home Phone: May I leave a message?
Cell Phone: Work:
Email: _

- 5. SS#:

- 6. Age: Birth date:
Gender: Do you identify as
transgender?

- 7. Education (grade/degree completed, any post secondary):

- 8. Current
Occupation:

- 9. Person to alert in the event of a medical emergency:
Address: _
Relationship to you: Phone:

- 10. Family Doctor:
Phone:

- 11. Relationship status (circle one): Single Married Partnered Separated Divorced Widowed If not married, are you currently in a relationship? " Yes " No
If yes, for how long?

- 12. name: Spouse's/partner's Phone:

- 13. Children (gender, age):

APPENDIX C

FOLLOW-UP CALL AT 4 WEEKS

Fundamentally, this is an open conversation with subjects to ascertain the aftermath effects of the two ketamine sessions.

Questions that are included will focus on:

Any adverse effects on subjects or infants: Have you felt or noticed and problems with your physical state; or your emotional state since your ketamine sessions? If so, do you attribute these to your ketamine experiences.

Were there positive effects that you have noted?

Have you noticed any changes in your infant since your ketamine experiences? Do you attribute these to ketamine?

Difficulties in resuming breast feeding: Did you have any difficulties with your infant as a result of the suspension of breast feeding? How long did this last if there were problems? Do you have a view of how long suspension of breast feeding is tolerable to you? To your infant?

Have you experienced any psychological difficulties or insights you have not discussed in the prior 4 weeks of follow-up?