RESEARCH PROTOCOL

Study Title	**Po**stpartum depression after **C**esarean delivery: **Ket**amine as a preventative intervention. A feasibility pilot-study.
Short Title	The PoCKet pilot.
Principal Investigator	Dr David Thomas Monks MBChB FRCA MSc, Assistant Professor, Department of Anesthesiology, Washington University School of Medicine, 660 S Euclid Avenue St. Louis. 314-601-1572 dmonks@wustl.edu
Co-Investigators	Dr Arvind Palanisamy, MBBS FRCA MD Associate Professor of Anesthesiology and Obstetrics and Gynecology, Division Chief of Obstetric Anesthesiology, Washington University School of Medicine. Dr Shannon Lenze, PhD Assistant Professor of Psychiatry, Director of Research, Perinatal Behavioral Health Service, Washington University School of Medicine. Dr Michael Avidan, MBBCh FCA(SA) Dr Seymour and Rose T. Brown Professor of Anesthesiology, Chair of the Department of Anesthesiology, Washington University School of Medicine. Dr Preet Mohinder Singh, MBBS Assistant Professor, Department of Anesthesiology, Washington University School of Medicine.
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SYNOPSIS

Study Title	**Po**stpartum depression after **C**esarean delivery: **Ket**amine as a preventative intervention. A feasibility pilot-study (PoCKet Pilot).
Primary Objective	To assess the feasibility of the study by establishing: a) the incidence of PPD in our cohort; b) the acceptability to eligible patients; c) the ability of the investigative team to collect the data and; d) the tolerability of the interventions.
Hypothesis	We hypothesize that ketamine reduces the incidence of postpartum depression (PPD) when administered at cesarean delivery and that the subcutaneous route is well tolerated and has a favorable pharmacokinetic profile.
Study Period	Planned enrolment duration: 52 weeks Planned study duration: 58 weeks
Number of Participants	60 patients (20 in each of the subcutaneous [SC], intravenous [IVI] and control [P] groups)
Study Intervention	Patients in each group will receive both subcutaneous (s/c) and intravenous (i.v.) administration of their corresponding injectate shortly after delivery of their baby. The injectate will consist of either 0.9% Sodium Chloride (N/S) or 50 mg/ml ketamine (Ket) depending on their group allocation. The s/c injectate will be administered undiluted whereas the i.v. injectate will be diluted to make up a 40 ml infusion. **Groups** — **s/c injectate** — **i.v. injectate** **SC:** Ket — N/S **IVI:** N/S — Ket **P:** N/S — N/S
Study Design	A randomised, double-blind, placebo-controlled feasibility pilot study
Eligibility Criteria	**Inclusion criteria** 1. Term pregnancy 2. Age 18-45 years of age 3. Scheduled cesarean delivery under neuraxial anesthesia **Exclusion criteria** 1. ASA classification IV or V 2. History of psychotic episodes 3. History of allergy to ketamine 4. Inability to communicate in English or any other barrier to providing informed consent
Measurements	a) Psychosocial stress (Antenatal Risk Questionnaire [ANRQ]) b) Weight (kg) and height (m) c) Time of delivery of baby d) Total intraoperative dose of analgesic/sedative medication e) Baseline and intraoperative vital signs f) Maximum intraoperative pain (NRS) g) 48-hour total opiate consumption (morphine equivalents) h) Apgar scores at 1 and 5 minutes postpartum i) Admission to NICU

	j) Pain originating from surgical site (NRS 0-10): 2, 6, 24 and 48 hours and 21 and 42 days postpartum. k) Edinburgh Postpartum Depression Scale (EPDS) and Generalized Anxiety Disorder 7-item (GAD-7) Scale: Day of surgery and postpartum days 1, 2, 21 and 42 l) Plasma concentrations of ketamine at baseline, 20, 40 and 100 minutes after administration m) Breastfeeding success (Y/N): postpartum days 1 and 2 n) Adverse effects, intraoperatively and at 2 and 6 hours postpartum (absent, mild, moderate or severe)
Statistical Methodology	Descriptive statistics will be employed to present the demographic data. Continuous variables will be summarized using means (SD) or medians (IQR), as appropriate. After construction of the concentration-time curves for each patient, the peak plasma concentration and area under the concentration-time curve will be summarized overall and associations with both antidepressant effect and incidence of adverse symptoms will be explored. NONMEM© 7.4 (ICON Development Solutions) software will be utilised to assess pharmacokinetic profile of ketamine by each route.

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1. BACKGROUND AND SIGNIFICANCE

1.1 Postpartum depression (PPD)

PPD is one of the most common perinatal medical complications and can have a detrimental effect on both mother and baby. Suicide exceeds hemorrhage and hypertensive disorders as a cause of maternal mortality[1] and maternal psychopathology interferes with the parent-infant relationship[2]. It has been estimated to have a period prevalence of 19.2% in the first 3 postpartum months. The rapid decline in reproductive hormones is thought to contribute to the development of PPD in susceptible women, although the specific pathogenesis is unknown. The American College of Obstetricians and Gynecologists[3] recommend that all women should be routinely screened for depressive symptoms in the perinatal period. The strongest risk factor is history of pre-existing mood disorder and Robertson et al.[5] list additional risk factors (Table 1) for PPD in the postpartum period.

• Depression during pregnancy • Traumatic birth experience • History of depression • Anxiety during pregnancy	• Breastfeeding problems • Preterm birth/infant admission to neonatal intensive care (NICU)

Table 1: Risk factors for PPD

1.2 Ketamine's anti-depressant effect

Ketamine, a phencyclidine derivative, is a non-competitive antagonist at the N-methyl-D-aspartic acid (NMDA) receptor that is commonly used as an anesthetic or sedative agent and has proven analgesic effect after a variety of surgeries including CD[6], where it has also been shown to reduce shivering[7]. It has been demonstrated to have a rapid anti-depressant effect in treatment-resistant depression[8] outside of pregnancy. The most commonly employed intravenous (IV) dose for this purpose is 0.5 mg/kg over 40 minutes, as single or repeated infusions. It has been postulated that prolonged blockade of NMDA receptors causes long-term changes in signal transduction leading to sustained clinical improvement, some investigators have explored longer term infusions such as those used to treat chronic pain[9]. A recent pilot study assessing the feasibility of a 96-hour (~0.5mg/kg/hr) infusion[10] compared with a single 40-minute (0.5 mg/kg) infusion suggested a trend toward greater efficacy in the prolonged infusion but confirmation of a statistically significant result is awaited.

1.3 Ketamine and PPD

This promising anti-depressant effect has prompted investigation of ketamine as a preventative measure in patients undergoing CD. There have been 2 studies to date[11,12], one which failed to demonstrate any benefit from a bolus dose of 0.25 mg/kg and one which documented a large reduction (1 and 22% in the treatment and control, respectively) in the (6 week) period prevalence of postpartum depression after a 4 mg/kg dose of ketamine over 50 hours (~0.08 mg/kg/hr).

The prolonged IV infusion, in the Jianxin (2015)[12] study, was achieved by adding the ketamine to a sufentanil patient-controlled analgesic (PCA) pump with a background infusion. This PCA pump is a standard part of their post-cesarean analgesic regimen. In our institution, it is standard practice to discontinue IV infusions and to remove IV cannulae as early as it is safe to do so. This practice is essential to the attempts to enhance postoperative recovery and aid mother's bonding with their babies and facilitate their early-

life care. This reflects patients' expectations and preferences and is in line with other maternity units across North America and Europe.

The natural course of PPD varies and, although it may resolve spontaneously within weeks, approximately 20% of women with PPD still have depression at 12 months and beyond. As many as 13% will still have depressive symptoms at 2 years and 40% will have a relapse[13]. Considering the maternal suffering, disruption to the family, potential impairment of the social, emotional, and cognitive development of the child[14], and the rare cases of infanticide and suicide caused by PPD, the impact on families and society as a whole is difficult to overemphasize. An intervention that promises such a large reduction in this devastating disease warrants extensive research. In an attempt to achieve the benefit demonstrated by Jianxin et al. whilst employing methods more acceptable to our patients we have designed a pilot study to assess the feasibility of our study design and collect preliminary tolerability and efficacy data on ketamine administered by two alternative routes: 40-minute IV infusion (i.v.) and subcutaneous (s.c.) injection.

2 OBJECTIVES

2.1 To determine the feasibility of performing this study at our institution

2.2 To determine the pharmacokinetic profiles of ketamine when administered as a subcutaneous injection and an intravenous infusion at cesarean delivery

2.3 To obtain preliminary data to inform the design of a randomized controlled trial to assess the efficacy of ketamine as a preventive intervention at cesarean delivery against PPD

3 PATIENT SELECTION

3.1 Inclusion criteria:
- 3.1.1 Term pregnancy
- 3.1.2 Age 18-45 years of age
- 3.1.3 Scheduled cesarean delivery under neuraxial anesthesia

3.2 Exclusion criteria:
- 3.2.1 ASA classification IV or V
- 3.2.2 History of psychotic episodes
- 3.2.3 History of allergy to ketamine
- 3.2.4 Inability to communicate in English or any other barrier to providing informed consent

3.3 Inclusion of women and minorities:
- 3.3.1 Eligible pregnant women of all ethnicities and cultures presenting to the Barnes Jewish Hospital Labor & Delivery floor will be invited to participate in this research

4 REGISTRATION PROCEDURES

4.1 Confirmation of patient eligibility
- 4.1.1 We will screen all patients scheduled for cesarean delivery and confirm their eligibility by assessing their: i) age; ii) gestational age; iii) medical history and; iv) allergy history.

4.2 Assignment of unique participant number
- 4.2.1 Each patient will be identified with a unique participant number (UPN) for this study. All data will be recorded with this identification number on the appropriate case report form (CRF).

4.3 Randomization
- 4.3.1 Patients will be randomly assigned to one of the three groups: SC, IVI or Control. The randomization will be performed in 1:1:1 ratio in blocks of 6, with no stratifications.

5 STUDY DESIGN

5.1 This will be a double-blinded, placebo-controlled, feasibility pilot study. The primary outcomes are related to the ability of the study procedures to gather data on the interventions' efficacy in preventing postpartum depression. Successful attainment of the following feasibility milestones (FM) is necessary to justify proceeding with a pragmatic clinical trial:
- 5.1.1 **FM1**: Establish that the incidence of PPD in our cohort is >10%
- 5.1.2 **FM2**: Achieve the recruitment of >50% of approached patients to demonstrate feasibility for an RCT
- 5.1.3 **FM3:** Ensure that the design of assessments and data collection make it possible to achieve a complete dataset in >90% of participants

5.1.4 **FM4:** Ascertain that none of chosen routes of administration of ketamine is intolerable to patients, as defined as the incidence of one or more severe side effects experienced by >10% of participants in that study arm.

6 STUDY PROCEDURES

6.1 Participants will be assigned to one of three intervention groups (Table 2).

Groups	***Subcutaneous injectate***	***Intravenous injectate****
SC (n=20)	50 mg/ml ketamine	0.9% Sodium Chloride
IVI (n=20)	0.9% Sodium Chloride	50 mg/ml ketamine
P (n=20)	0.9% Sodium Chloride	0.9% Sodium Chloride

Table 2: Intervention groups. *****the i.v. injectate will be diluted up to a 40 ml infusion.

6.2 Participants will have baseline data (Table 3) recorded on the relevant case report form on the day of delivery. This data will include demographics to assess the performance of randomization procedures as well as characteristics that have been demonstrated to confer an increased risk of PPD. The patient will be prepared for cesarean as per institutional protocols.

Measure	**Units/values**
Age	Years
Height	Metres
Weight (day of surgery)	Kilograms
Gestational age	Weeks
Ethnicity	White, Black/African American, Asian, Native American/Alaskan natives, Native Hawaiian, Pacific Islander, Hispanic/Latino
Insurance status	Insured/uninsured
Psychiatric history	PPD, major depressive disorder (MDD), anxiety, premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD), mood disorder, personality disorder, psychotic disorder
Current anxiety and depressive symptoms	EPDS and GAD-7
Psychosocial stress	ANRQ

Table 3: Baseline data

Once an adequate sensory block is achieved, surgery will commence. Upon delivery of the baby, 0.01 ml/kg of the *"subcutaneous injectate"* will be injected subcutaneously and the *"intravenous injectate"* will be made up to a 40ml infusion (Table 4) and commenced at 60 ml/hr. Both injectates will be administered/initiated approximately 0 - 5 minutes after delivery by the anesthetic provider via one of the cannulae that they will be using for standard patient care. The intravenous study infusion will be prepared by a member of the investigative team, who will not be involved in data collection.

Add 0.01 ml/kg of the "IVI *study solution"* to a 60ml syringe and use 0.9% sodium chloride to dilute the solution to 40ml.

Table 4: Instructions for preparing the "IVI *study infusion"*

Measurements:

1. Baseline data
2. EPDS and GAD-7 scores at baseline and approximately 1, 2, 21 and 42 days postpartum

3. ANRQ at baseline
4. Time of delivery of baby
5. Total intraoperative dose of any analgesic/sedative medication
6. Incidence of hypo- or hypertension (systolic BP < 80 or > 170 mmHg, respectively) and brady- or tachycardia (pulse < 40 or > 120 bpm, respectively)
7. Maximum intraoperative pain (numerical rating scale [NRS], 0-10)
8. Incidence of the signs/symptoms in Table 5 will be assessed intraoperatively and approximately 2 and 6 hours after delivery. The presence of each adverse effect will be assessed using a 4-point scale (absent, mild, moderate, severe).

Nausea	Shivering	Blurred vision
Vomiting	Anxiety	Diplopia
Pruritus	Euphoria	Nystagmus
Dizziness	Hallucinations	
Sedation	Amnesia	

Table 5: Adverse effects

9. Surgical site pain (NRS) at 2, 6, 24 and 48 hours, as well as 21 and 42 days, postpartum.
10. Opiate consumption in the first 48 hours (measured in morphine equivalents) will be calculated.
11. Plasma concentrations of ketamine at baseline and approximately 20, 40 and 100 minutes postpartum.

7 STUDY SCHEDULE

Study Event	**Baseline**	**Perioperative (approximate minutes after delivery)**			**Postoperative (approximate hours after delivery)**				**Outpatient (approximate days after delivery)**	
		20	**40**	**100**	**2**	**6**	**24**	**48**	**21**	**42**
Informed consent	✓									
Eligibility/ Demographics	✓									
Randomization	✓									
Blood Sample Collection	✓	✓	✓	✓						
Maximum intraoperative pain (NRS, 0-10) score				✓						
Adverse Effects				✓	✓	✓				
Breastfeeding Success							✓	✓		
Surgical Site Pain (NRS)					✓	✓	✓	✓	✓	✓
EPDS	✓						✓	✓	✓	✓
GAD 7	✓						✓	✓	✓	✓
ANRQ	✓									

Table 6: Study schedule

8 OBSERVATIONS AND MEASUREMENTS

8.1 Primary outcome measures

- 8.1.1 **FM1**: Establish that the incidence of PPD in our cohort is >10%
- 8.1.2 **FM2**: Achieve the recruitment of >50% of approached patients to demonstrate feasibility for an RCT
- 8.1.3 **FM3:** Ensure that the design of assessments and data collection make it possible to achieve a complete dataset in >90% of participants
- 8.1.4 **FM4:** Ascertain that neither of the chosen routes of administration of ketamine are intolerable to patients, as defined as the incidence of one or more severe side effects experienced by >10% of participants in that study arm.

8.2 Secondary outcome measures

- 8.2.1 Intraoperative supplementary analgesia
- 8.2.2 Intraoperative hypo/hypertension and brady-/tachycardia
- 8.2.3 Maximum intraoperative pain (NRS)
- 8.2.4 Adverse effects intraoperatively and at approximately 2 and 6 hours postpartum
- 8.2.5 Plasma concentrations of ketamine at baseline and approximately 20, 40 and 100 minutes postpartum. Samples will be centrifuged and the extracted plasma samples will be stored at -80 degrees Celsius before transfer to the metabolomics laboratory at Washington University for ketamine assay.
- 8.2.6 Total opiate consumption in the first 2 days postpartum
- 8.2.7 Surgical site pain (NRS 0-10), by face-to-face or telephone interview, at 2, 6, 24 and 48 hours after delivery and on postpartum days 21 and 42.
- 8.2.8 EPDS and GAD-7 on postpartum days 1 and 2, by face to face interview, and days 21 and 42, by telephone interview.
- 8.2.9 Apgar scores
- 8.2.10 Admission to NICU
- 8.2.11 Breastfeeding success (Y/N) on post-operative days 1 and 2

9 STATISTICAL METHODS

9.1 Sample size and analysis

No formal sample size has been performed as this is a pilot designed to establish the feasibility of an RCT. Preliminary data from this study will be used to inform the sample size calculation for the subsequent clinical trial. Descriptive statistics will be employed to present the demographic data. Continuous variables will be summarized using means (SD) or medians (IQR), as appropriate. After construction of the concentration-time curves for each patient, the peak plasma concentration and area under the concentration-time curve will be summarized overall and associations with both antidepressant effect and incidence of adverse symptoms will be explored.

9.2 Pharmacokinetic analysis

NONMEM® 7.4 (ICON Development Solutions) software will be utilised to assess pharmacokinetic profile of ketamine by each route.

10 REGULATORY AND REPORTING REQUIREMENTS

10.1 Definitions

Adverse event (AE): Any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Serious adverse event (SAE): Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e. a substantial disruption of a person's ability to conduct normal life functions).
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent on of the outcomes listed above

Unanticipated problem: Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, and (b) the characteristics of the subject population being studied; related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Noncompliance: Failure to follow any applicable regulations or institutional policies that govern human subject's research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

10.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

10.3 Timeframe for reporting required events

These events must be reported to the IRB within 10 working days of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within 1 working day of the occurrence of the event or notification to the PI of the event.

Adverse events: The investigator will closely monitor subjects for evidence of adverse events. We review data on a regular basis. All adverse events will be reported and followed until satisfactory resolution. The description of the adverse experience will include the time of onset, duration, intensity, etiology, relationship to the study drug (none, unlikely, possible, probable, highly probable), and any treatment required.

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