Neuraxial Preservative Free Morphine for Normal Spontaneous Vaginal Delivery:
A Prospective Double Blind Randomized Control Trial
Duramorph Study Design: Prospective, Randomized Double Blinded
PI: Daniel Katz, MD
NCT04017442
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Duramorph Study Design: Prospective, Randomized Double Blinded

Unique Protocol Identification Number:

National Clinical Trial (NCT) Identified Number: NCT04017442

Principal Investigator: Daniel Katz

IND/IDE Sponsor:

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

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STATEMENT OF COMPLIANCE

Provide a statement that the trial will be conducted in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP) and applicable state, local and federal regulatory requirements. Each engaged institution must have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before implementation. Select one of the two statements below. If the study is an ***intramural*** *NIH study, use the second statement below:*

1. The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

    - United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

    National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.
    OR
2. The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the [specify NIH Institute or Center (IC) [Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.
    For either option above, the following paragraph would be included:
    The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Duramorph Study Design: Prospective, Randomized Double Blinded	
Study Description:	Prospective double blind randomized control trial	
Objectives:	Primary Objective:	Analyze impact of epidural morphine on pain management for vaginal delivery VD
	Secondary Objectives:	Analyze impact of epidural morphine on recovery and depression
Endpoints:	Primary Endpoint:	Opiate consumption at 24 hours
	Secondary Endpoints:	Pain score at 24 hours, obstetric revoery score at 24 hours, ediburgh post partum depression scale at 6 weeks, breast feeding success at 1 week
Study Population:	Pregnant women over 18	
Phase:	4	
Description of Sites/Facilities Enrolling Participants:	KP2 Labor floor at Mount Sinai Hospital	
Description of Study Intervention:	Epidural morphine 2mg vs placebo	
Study Duration:	4 years	
Participant Duration:	6 weeks	

1.2 SCHEMA

1. Obtain consent
2. 1 hour delivery administer study drug or placebo
3. 24 hours after collect data on opiate administration, pain score, and recovery score
4. 1 week after administration call patient inquire about breast feeding
5. At 6 weeks after administration call patient and administer post partum depression screen

1.3 SCHEDULE OF ACTIVITIES (SOA)

1. Obtain consent
2. 1 hour delivery administer study drug or placebo
3. 24 hours after collect data on opiate administration, pain score, and recovery score
4. 1 week after administration call patient inquire about breast feeding
5. At 6 weeks after administration call patient and administer post partum depression screen

2 INTRODUCTION

2.1 STUDY RATIONALE

There is no current standard of care for post vaginal delivery pain. Many different options exist, however, their impact on minimizing opiate utilization have been minimal. As such, we are investigating the utility of a single dose of preservative free morphine on pain scores in the post partum period.

2.2 BACKGROUND

There is no gold standard for pain management in NSVD. There is some evidence that preservative free morphine is effective at pain relief for cesarean deliveries. The relationship between pain and epidural morphine for NSVD has not been investigated.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risks can include nausea, vomiting, itching, respiratory depression

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Benefits include less oral and IV opiate use which also cause nausea, itching and respiratory depression. Benefits may also include a faster recovery and more breast feeding. The risks of this dose of morphine are small and have been used for cesarean delivery for decades.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
	Opiate consumption at 24 hours	Opiate use should be minimized due to side effects
Secondary		
	Pain score at 24 hours Recovery score at 24 hours Breast feeding rate at 1 week Post partum depression screen at 6 weeks	Better pain control is good endpoint, as is recovery. Breastfeeding can have long term impacts on both mom and baby and it's impact should be investigated. Depression is a major issue post partum and controlling pain in the immediate post partum period may help with that.
Tertiary/Exploratory		

4 STUDY DESIGN

4.1 OVERALL DESIGN

Double blind, prospective, randomized control trial

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

When investigating the impact of a medication on pain, opiate consumption, etc, it is important for the study to be blinded and randomized to avoid bias.

4.3 JUSTIFICATION FOR DOSE

This dose is commonly administered to pregnant women for cesarean delivery. It has an excellent safety profile and a long history of use.

4.4 END OF STUDY DEFINITION

Patients complete their involvement after their 6 weeks post partum depression screen

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

18 years old, pregnant, presenting for VD

5.2 EXCLUSION CRITERIA

Refusal of neuraxial anesthesia, allergy to morphine, patients with chronic pain syndromes or chronic opiate use.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable for this study.

5.4 SCREEN FAILURES

Patients are consented when they have adequate pain control and are in labor. Due to patient convenience patients may consent to participate but not be randomized based on their time of delivery. These patients will be kept in a separate log.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

We will use the clinical anesthesia team to inform us of potential patients. They have been educated about the study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Epidural morphine 2mg

6.1.2 DOSING AND ADMINISTRATION

2 mg (4ml) will be administered one hour after the patient has their VD. It will be administered through their in situ epidural

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Investigational Drug Service stocks the Pyxis machine with the study drug. it uses real time automated biometric safety protocols to ensure only those able to administer the study drug are allowed to remove it

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

PI attached to IRB application. it is a brown ampule with 10mg total in the vial.

6.2.3 PRODUCT STORAGE AND STABILITY

It is stored in the Pyxis machine as per requirements

6.2.4 PREPARATION

After removal from the Pyxis machine the study drug is steriley drawn up into a syringe and labeled "study drug". This is then handed off to a different member of the study team to administer. The remainder is returned to the drug lockbox as per protocol

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All patients presenting for VD are eligible and the clinical teams are trained in implicit bias and have had special education from the research team for this study. Given the randomization we cannot demand

that any specific group be targeted for recruitment. We want an equitable and balanced sample for our study.

6.4 STUDY INTERVENTION COMPLIANCE

Each step is recorded in either the datasheets or Pyxis logs. After the administration all that remains is data collection from the patients. Given that we contact patients at the required times we expect a high level of compliance.

6.5 CONCOMITANT THERAPY

6.5.1 RESCUE MEDICINE

Any patients on opiates or with an allergy to morphine are excluded and as such there is no risk for synergistic effects of the study drug. As per our CD protocol, we provide the same rescue doses of medications for morphine including ondanstetron, diphenhydramine, and nalxone all as needed.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Should we experience any cases of respiratory depression we will stop the study and review the case.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants may withdraw from the study at any time by notifying the study team and/or the PI either verbally or in written form.

7.3 LOST TO FOLLOW-UP

Given that one of our endpoints is 6 weeks out we expect to loose some patients to follow up. This will impact our findings, however, our study is powered for our primary endpoint which is opiate consumption at 24 hours. We expect little or no followup loss for this endpoint.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

At 24 hours we will get a likert pain score, as well as a recovery score. We will also obtain opiate consumption for this time.

8.2 SAFETY AND OTHER ASSESSMENTS

At one week we will ask patients about breast feeding. At 6 weeks we will ask about depression

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse events include nausea and itching

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious adverse event would be respiratory depression requiring naloxone administration

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

Classification of an adverse event is based on symptomatology type as described above.

8.3.3.1 SEVERITY OF EVENT

As above, severity is determined by need to administer rescue medications and type.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

We will examine each case and determine relationship to the study intervention.

8.3.3.3 EXPECTEDNESS

We expect to have cases of nausea and itching, we anticipate no cases of respiratory depression

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Patients are monitored according to post partum protocols. The areas the patients recover are all equipped to manage patients after receiving neuraxial morphine.

8.3.5 ADVERSE EVENT REPORTING

We receive reports from patients about their AEs on follow up or from the clinical team if they bring it up.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

All patients are monitored for respiratory depression. All cases of this are reported to our internal PI committee and reviewed independently.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

All AEs are reported to participants.

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

There are no unanticipated problems with this study, however, should any issue occur the PI will be available to discuss

8.4.2 UNANTICIPATED PROBLEM REPORTING

At any time any participant, clinical team member, or study team member can report and event to the PI.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Those that may impact patient care and well being will be reported to all participants.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

Opiate consumption at 24 hours (Wilcoxon Rank Sum)

- Secondary Efficacy Endpoint(s):

Recovery score at 24 Hours (Wilcoxon Rank Sum)
Breast feeding at 1 week (Chi Square)
Depression screen at 6 weeks (Wilcoxon Rank Sum)

9.2 SAMPLE SIZE DETERMINATION

Based on other works it was determined that for a 25% reduction in opiate utilization we needed 60 patients for each group. To account for drop off we will recruit 150 patients per group for a total of 300 patients

9.3 POPULATIONS FOR ANALYSES

This will be intention to treat for all randomized participants.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Wilcoxon rank sum for continous variables, chi square for categorical

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Wilcoxon rank sum

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Recovery score and depression score: Wilcoxon Rank Sum, Breast feeding: Chi square

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Given randomization we will simply report, not anlayze

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

N/A

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Will be performed using secured encrypted software (RedCap) and SPSS software

9.4.9 EXPLORATORY ANALYSES

Not applicable

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

After the patient is comfortable from their epidural the clinical team will get assent for the research team to approach the patient. The research team will then consent the patient using standardized process in compliance with IRB protocols

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

N/A

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

As per IRB standard protocol

10.1.2 STUDY DISCONTINUATION AND CLOSURE

Upon notification of withdrawal participants can either elect to have their data destroyed, or allow the research team to analyze data obtained.

10.1.3 CONFIDENTIALITY AND PRIVACY

All data is gathered via a study ID with a linking code. ONLY the PI has access to the code which is stored in a locked office on a locked computer that is password protected and encrypted. As such the information is de-identified.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

N/A

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Daniel Katz	
daniel.katz@mountsinai.org	
732-322-6675	
1 Gustave L Levy Place Box 1010	
KCC 8th Floor NY, NY 10029	

10.1.6 SAFETY OVERSIGHT

The PI will examine all cases of AE and SAE

10.1.7 CLINICAL MONITORING

All patients are monitored as per hospital protocols.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The PI will handle all study related issues in regards to QA and QI Except for respiratory depression events. These will be investigated by the departmental QI committee.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

All data are collected on de-identified forms. These are then put into a de-identified Redcap secured database. The PI will review records on an ad hoc basis for completeness and accuracy.

10.1.9.2 STUDY RECORDS RETENTION

Will be kept for 5 years after completion and then destroyed

10.1.10 PROTOCOL DEVIATIONS

10.1.11 PUBLICATION AND DATA SHARING POLICY

We will not be sharing individual results with patients, however, we will publish our results in a medical journal.

10.1.12 CONFLICT OF INTEREST POLICY

As per the FCOI office of our institution

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance

CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

11 REFERENCES