Prevention of Persistent Pain and Opioid Use in Mothers – POMS

NCT03472521

February 11, 2020

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1. PURPOSE OF THE STUDY

a. Brief Summary

While most women have uneventful recovery after childbirth, we have identified 20% who are at risk for prolonged pain and delayed opioid cessation and functional recovery with usual care in our previous work. Moderate to severe pain on postpartum day 1-2 is a significant predictor of being in the risk group. We plan to test an intervention of low dose gabapentin or placebo on the time that women require opioid analgesia. We hypothesize that outpatient treatment with gabapentin in high risk women (postoperative day one pain score (NRS > 6 x 2) despite usual multimodal analgesia) will lead to reduced need for opioid, less pain and more rapid functional recovery.

b. Objectives

We will determine whether treatment of high risk women with gabapentin in the outpatient setting will reduce time to opioid cessation.

c. Rationale for Research in Humans

Pain during the postpartum period is unique in humans and cannot be studied in animals.

2. STUDY PROCEDURES

a. Procedures

Patients who deliver at Lucille Packard Hospital who report at least 2 NRS pain scores of 6-10 despite receiving the normally prescribed multimodal analgesic protocol will be approached for enrollment. They will be offered gabapentin starting at 300 mg tid or placebo tablets in addition to their usual multimodal pain regimen (scheduled acetaminophen, a non-steroidal anti-inflammatory and prn oxycodone). Assignment to treatment group will be according to a randomization table available only to the research pharmacist. All patients will have access to Dr. Flood by email or text for optimal titration of study drug or any significant problems. They will be advised to titrate off their opioid first, followed by study drug, followed by non-steroidal anti-inflammatory medications and acetaminophen.

All study subjects will receive a weekly survey with pain report, medication use and side effects for a maximum of 12 weeks or until pain report they report that they have recovered to their usual state of health. In addition the weekly survey will include PROMIS questionnaires for sleep, fatigue, depression, anxiety and physical. The subject will receive a $10 gift card by email when each weekly questionnaire is completed. The primary outcome variable will be time to opioid cessation. Secondary outcomes will be pain report, functional recovery PROMIS questionnaire responses, breast feeding, and anticipated side effects of opioids including nausea, constipation, and fatigue.

Subjects will be offered the opportunity to wear a wrist worn fitness tracking device. The device will track their daily steps taken and sleep efficacy. The results will be compared between the active and placebo groups at the end of the study. Baseline expectations for mobility and sleep efficacy will also be recorded and published as this information is scant in the literature. The device will be theirs to keep at the end of the study.

To evaluate the effect of the intervention on the participant's longer-term wellbeing, those who have agreed to be contacted for future studies on the original consent will be contacted with an email/text script that is attached one year after delivery. If they consent, the questionnaire that that had completed weekly during the 12 week study will be sent to them through Redcap.

b. Procedure Risks

Gabapentin is a medication that is commonly used for breakthrough pain in women immediately post-partum at LPCH and in the treatment of epilepsy throughout pregnancy. It is a commonly used analgesic for post-operative pain and chronic neuropathic pain and fibromyalgia outside of pregnancy. There are mixed data on its immediate inpatient post partum analgesic efficacy but has not been studied for longer term outpatient recovery benefit for opioid cessation or pain management in this high risk group..

Gabapentin has a low molecular weight and minimal protein-binding in plasma. It has penetration into breast milk, with an M/P ratio of 1.1 (range 0.5–2.0) [1-3]. Maternal gabapentin doses up to 2100 mg daily produced low infant serum concentrations between 1 and 6% of the mother's levels, and with no adverse effects in the neonates [1-3].

1. Kristensen JH, Ilett KF, Hackett LP, et al. Gabapentin and breastfeeding: a case report. J Hum Lact 2006;22(4):426–8.
2. Hovinga CA, Pennell PB. Antiepileptic drug therapy in pregnancy II: fetal and neonatal exposure. Int Rev Neurobiol 2008;83:241–58.
3. Ilett K, Kristensen J. Drug use and breastfeeding. Expert Opin Drug Saf 2005;4(4):745–68.

c. Use of Deception in the Study

Deception will not be used.

d. Use of Audio and Video Recordings

There will be no audio or video recording.

e. Alternative Procedures or Courses of Treatment

This study drug (gabapentin or placebo) will be added in addition to the usual standard of care. In addition, all subjects will be under the supervision of a pain management specialist who will provide an enhanced level of care. There is no other routine treatment that will be prevented by virtue of the study. If the patient's pain is not well maintained, they will be referred to the pain management clinic for further evaluation where they would be offered any care deemed necessary regardless of study enrollment.

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

If the patient wishes to continue active treatment, they will be referred to pain management for further care.

g. Study Endpoint(s)

The study endpoint will be the day on which there is a report of pain no different than baseline, no analgesic requirement and patient reported functional recovery. The participant will be recontacted at 12 - 18 months for their permission to receive another survey.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

Our previous work has used daily follow-up after delivery to determine norms for pain and opioid cessation with functional recovery (2). After cesarean delivery, 27 [19 to 40] days are required for pain and opioid-free functional recovery, 9 [5 to 12] for opioid cessation, 16 [11 to 24] for pain resolution, and 21 [14 to 27] days for functional recovery, respectively in the general population (median [interquartile range (IQR)]).[1]

Two factors allowed for identification of pain burden, post-operative day 1 NRS score > 6 and labor induction prior to cesarean delivery. High reports of labor pain immediately cesarean delivery has previously been found to be predictive of poorer outcome. NIH PROMIS anxiety score and Rand (36) item Health Survey SF36 score was predictive of delayed opioid cessation in addition.[2]

1. Komatsu R, Carvalho B, Flood PD. Recovery after Nulliparous Birth: A Detailed Analysis of Pain Analgesia and Recovery of Function. Anesthesiology. 2017 Oct;127(4):684-694.
2. Komatso R, Carvalho B, Flood P. Prediction of pain, analgesia requirement and recovery of function after childbirth. Br J Anaesth 2018; 121:417-26.

b. Findings from Past Animal Experiments

N/A

4. DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY

a. Commercial Drugs, Biologics, Reagents, or Chemicals

Commercial Product 1	
Name:	Gabapentin
Dosage:	300-1200 mg tid
Administration Route	Oral
New and different use? (Y/N)	No

5. Disinfection Procedures for Medical Equipment Used on Both Humans and Animals

N/A

6. Participant Population

a. Planned Enrollment

78 patients will be enrolled, 39 in active and 39 in placebo arm

b. Age, Gender, and Ethnic Background

All subjects will be women who have given birth by cesarean section within on week, age >18 years with any ethnic background who can understand English well enough to give consent and answer written questionnaires administered in English.

c. Vulnerable Populations

N/A

d. Rationale for Exclusion of Certain Populations

All subjects will be women after childbearing which is most common in adults.

e. Stanford Populations

Laboratory personnel, employees, and/or students will not be specifically targeted for enrollment but will not be excluded if the meet entry criteria. They will be treated the same as any other subject.

f. Healthy Volunteers

No healthy volunteers

g. Recruitment Details

Subjects will be identified by review of Epic dashboard post cesarean section for at least 2 NRS scores > 6 and will be approached by study investigators to discuss interest in the study in the post-partum unit at Stanford Hospital. At that time, the prospective patient will be provided a handout with information on the purpose of the study, eligibility for the study, safety of gabapentin, and participant responsibilities should they enroll. The prospective patient can then review this material on their own time and consider whether they would like to discuss the study further.

h. Eligibility Criteria

i. Inclusion Criteria

Recent delivery, NRS > 6 on 2 occasions

ii. Exclusion Criteria

Allergy or intolerance to gabapentin. Age <18 years. Inability to complete study questionnaires and provide consent in English. Prepartum use of analgesics within one month. History of epilepsy.

i. Screening Procedures

Screening for NRS score will be using EPIC. Other criteria will be evaluated by investigator prior to consent.

j. Participation in Multiple Protocols

Subjects can be enrolled in more than one protocol if it does not require additional study drugs post partum. The subject will be asked if they are participating in any other studies.

k. Payments to Participants

Because the weekly questionnaire will take some time to complete, the subject will be paid a token $10 as an amazon gift card on completion of each weekly study questionnaire completed at home. They will be allowed to keep the fitness tracker at the completion of the 12 week study.

l. Costs to Participants

There will be no costs to the participant. Study drug will be provided free of charge.

m. Planned Duration of the Study

In our previous study, the range of days to study completion was 3-85 days. As such, we expect the maximal duration to be 12 weeks.

7. RISKS

a. Potential Risks

i. Investigational devices

None

ii. Investigational drugs

None

iii. Commercially available drugs, biologics, reagents or chemicals

Withdrawal precipitated seizure: will not be used in patients with epilepsy

Tumorigenic Potential- In epilepsy trials, with 2085 patient years of exposure, 10 new tumors were reported. It is unknown what the baseline incidence of these tumors would be in untreated patients and thus it is unknown whether this is above baseline.

Nursing mothers: Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, Neurontin should be used in women who are nursing only if the benefits clearly outweigh the risks. (package insert)

Gabapentin has a low molecular weight and minimal protein binding in plasma. It has penetration into breast milk, with an M/P ratio of 1.1 (range 0.5–2.0). Maternal gabapentin doses up to 2100 mg daily produced low infant serum concentrations between 1 and 6% of the mother's levels, and with no adverse effects in the neonates (1-3).

Hale's Medications and Mother's Milk lists Gabapentin in the "Safer" category out of categories of "Safer", "Moderately Safe", "Possibly Hazardous" and "Contraindicated

1. Kristensen JH, Ilett KF, Hackett LP, et al. Gabapentin and breastfeeding: a case report. J Hum Lact 2006;22(4):426–8.
2. Hovinga CA, Pennell PB. Antiepileptic drug therapy in pregnancy II: fetal and neonatal exposure. Int Rev Neurobiol 2008;83:241–58.
3. Ilett K, Kristensen J. Drug use and breastfeeding. Expert Opin Drug Saf 2005;4(4):745–68.
4. Thomas Hale and Hilary Rowe, Medications in Mother's Milk.Copyright © 2017 Springer Publishing Company, LLC

iv. Procedures

None

v. Radioisotopes/radiation-producing machines

N/A

vi. Physical well-being

Physical well being will be assessed regularly by the patient's obstetrician and through the study instruments.

vii. Psychological well-being

See above. Physical well being will be assessed regularly by the patient's obstetrician and by the pain management specialist through the study instruments and contact by patients if necessary.

viii. Economic well-being

There should be no economic cost.

ix. Social well-being

There should be no social cost.

x. Overall evaluation of risk

Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

b. International Research Risk Procedures

N/A

c. Procedures to Minimize Risk

The subjects will be followed with study instruments that indicate pain, opioid use, anxiety, function. The patient will specifically be asked about depression and anxiety. Any patient who indicates severe depression or anxiety will be immediately contacted by Dr. Flood, the study drug stopped and referred to the emergency room if indicated. The subjects will have the ability to immediately contact Dr. Flood should any emergency occur.

Identifiable data will be kept on encrypted systems and will only be accessible by study personnel.

d. Study Conclusion

The patient will use the study drug as long for 12-weeks or until the indicate complete recovery is indicated and the study terminated. Patients with significant side effects (most commonly sedation) will be advised to reduce dose and stop if required. If any patient's pain is uncontrolled, they will have the option to contact Dr. Flood and be seen by in pain clinic.

e. Data Safety Monitoring Plan (DSMC)

The Protocol Director will be the only monitoring entity for this study.

8. BENEFITS

Patients at high risk for prolonged pain, opioid use and poor functional recovery will be treated with study drug that may be helpful. Even those assigned to placebo will have the benefit of contact information for a pain specialist who can advise them in general pain management and follow up in clinic if needed.

9. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.