Protocol

1. **Title:**

Assessing Efficacy of Intramuscular Promethazine for the Treatment of Intrathecal Morphine Induced Pruritus

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2. **Investigators**

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3. **Abstract:**

This study aims to analyze a novel approach for prophylaxis against pruritis caused by neuraxial narcotics. Neuraxial narcotics are commonly used in obstetric patients for cesarean delivery to help with pain control over the first 24 hours after the surgery. Slappendel demonstrated intramuscular promethazine (IMP) was an effective treatment for intrathecal morphine induced pruritis (ITMIP).[1] No other studies evaluated IMP for treatment of ITMIP. The primary aim of this study will be to evaluate effectiveness of IMP prophylaxis of ITIMIP. Finding a prophylaxis for ITMIP other than naloxone, will allow for increased use of intrathecal narcotics and potentially decrease the use of systemic opioids in the initial post-operative period.

This study will use in-patients undergoing cesarean delivery at UF Health Shands Hospital in Gainesville, Florida.

4. **Background and Significance:**

Intrathecal morphine given during cesarean deliveries is one of the many ways providers currently help post-partum women with pain control. One major downside of intrathecal morphine is pruritus that occurs over the next 24-48 hours. During this time the mother should be enjoying time with her new infant, but instead is having to deal with the itching from the pain reliever we have given her. The

cause for the pruritus is not well known, but what is known is that anti-histamines such as diphenhydramine do not work. One class of medications known to help decrease ITMIP include mu opioid antagonists such as naloxone but some suggest there may be decreased analgesia when mu opioid antagonists are utilized. Further, due to the short half-life of naloxone, infusions of the medication must be used to adequately prevent recrudescence of symptoms in the setting of ITMIP. The related medication, nalbuphine, a partial opioid agonist has been found to be effective at treating ITMIP at the expense of increasing sedation and possibly nausea.[2-5] Nausea and vomiting is a frequent complication during cesarean delivery.

After reviewing the literature, three investigations have evaluated promethazine for prophylactic or treatment of neuraxial morphine induced pruritus. First, Eldor and colleagues found intramuscular promethazine was effective at reducing the incidence and severity of pruritis induced by epidural morphine.[6] Eldor conducted a randomized study among participants who had cesarean deliveries with epidural morphine. Those who received prophylactic IMP reported no pruritus while 35% of the control group experienced pruritus necessitating rescue treatment. Slappendel demonstrated that IMP was very effective at treating ITMIP.[1] Slappendel gave IMP to treat pruritus after varying doses of intrathecal morphine in orthopedic patients. Only one patient out of 143 subjects required escalation of therapy beyond IMP to treat ITMIP.[1] The article has not been confirmed nor refuted. This study was not blinded to the physician or the patient as this was their sole initial treatment for pruritus. Horta examined the potential of one of four different drugs to prevent ITMIP in patients undergoing cesarean delivery.[7] In this randomized study, 300 women undergoing elective cesarean delivery were randomized to one of five groups (intravenous alizapride 100mg, propofol 20, droperidol 1.25mg, promethazine 50mg or saline control). Horta failed to find a prophylactic effect of intravenous promethazine to prevent ITMIP. We would like to study IMP in post-partum patients that have just undergone a cesarean delivery in a blinded study to see if this is an effective prophylaxis for pruritus. This would benefit the mother to not itch while also allowing the morphine to continue with pain relief.

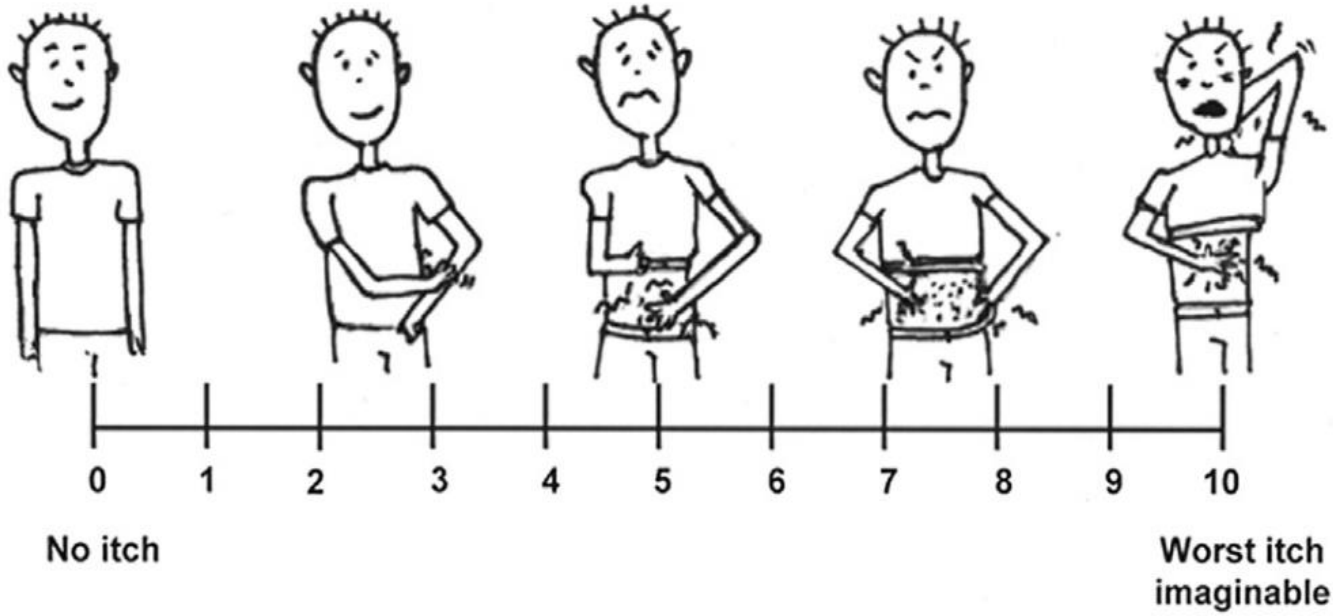
In 2018, Vice O'Con et. al[8] reviewed medications that were effective for treatment of post opioid pruritus and IM promethazine was not cited. They cited IV promethazine did not provide relief in this paper but could not find evidence for IM. Since very few medications actually work for this side effect, we would like to study IM promethazine in hopes to give another prophylaxis/treatment option that would not reverse the intrathecal narcotic. This paper cited that anti-dopaminergic medications did help decrease the pruritus but increased sedation in the forms given. Promethazine has a small amount of anti-dopaminergic activity and should decrease pruritus if it is truly a dopamine receptor mediated process.

5. **Specific Aims:** (research question/objectives)

Hypothesis: Prophylactic intramuscular promethazine does not decrease pruritus in post-partum females that received 100mcg intrathecal morphine.

Alternate Hypothesis: Prophylactic intramuscular promethazine does decrease pruritus in post-partum females that received 100mcg intrathecal morphine.

Pruritus will be quantified by the ItchyQuant Scale, developed and validated by CG Haydek as seen below.[9]



Secondary Analysis

-Promethazine does not increase sedation compared to placebo (RASS scale)

-Promethazine does not increase pain compared to placebo (DVPRS scale)

-Promethazine decreases nausea and vomiting (rated as none, mild, moderate, severe)

6. **Research Plan:**

Inclusion criteria:

1. Pregnant adult female patients of at least 18 years of age consenting to a cesarean birth;
2. Willing to consent to study.

Exclusion criteria:

1. Male patients;
2. Incarceration;
3. Inability to communicate with the investigators;
4. Allergies to any medications used in the study;
5. Possessing any contraindication to spinal anesthesia (lack of consent, elevated intracranial pressure, preexisting neurological disease, thrombocytopenia/coagulopathy, hypovolemia, infection at the site of the procedure);
6. Patients with an already prolonged QTc (>500 ms)
7. Any reason an investigator believes study participation would not be in the best interest of the potential subject.

DESIGN

STUDY PROCEDURES

Recruitment

Pregnant female patients already scheduled for a cesarean section operative procedure, as described in this protocol, will qualify for this study. The surgical schedule will be reviewed by the PI, Dr. Wendling, or one of the Co-I's, Drs., Lopez, Euliano, Andoniadis, or Mendoza as a part of their clinical duties. The PI and Co-I's are all Department of Anesthesiology staff and routinely work in the obstetrics unit, therefore, they all have a direct clinical relationship with the potential patients in this study. At least one of the PI or Co-I's will be working the obstetrics unit at the time of recruitment. Investigators (directly involved in clinical care) will review the surgical schedule and medical records of potential patients (as part of their routine clinical duties) greater than 1 day prior to surgery to more carefully evaluate the inclusion/exclusion for potential contraindications that could preclude or affect the patient's safety in the study. The extra step of oversight will help ensure potential patient safety prior to the surgeon approaching a patient to discuss the study.

Greater than 1 day prior to their scheduled surgery, all potential study participants identified as above will be contacted by phone and/or email if available by the PI or Co-I's. At this time, the PI or Co-I's will ask the patient if they are comfortable with a study coordinator contacting them and discussing a research study for which they qualify (phone script will be read). If the potential subject is interested, they will be provided the ICF. On the morning of surgery, additional questions and concerns will be addressed by one of the investigators (anesthesiologists) participating in the study and ICF will be completed. After obtaining written informed consent, women will be randomized into one of two groups: control or promethazine group. Method of randomization will be discussed below.

The hard copy consents will be stored in the study binder.

Patient typical day

The patient will come to the obstetric (OB) pre-operative holding area where we will obtain her medical history, perform a physical exam and consent her for the cesarean delivery. The patient will have already spoken with a study coordinator and/or PI/Co-I more than one day prior to arrival regarding potential participation in the study. The patient will be approached by one of the study team members (anesthesiologists). We will review the consent form, explaining that itching is a common side effect of the intrathecal morphine and we are trialing a medication that would prevent the itching. If the patient agrees to participate, we will obtain signed consent, contact the study coordinator to be prepared for questionnaires post-procedure and then obtain a blinded syringe from pharmacy for the treatment. Dr. Garvan will randomize the patient for the study to determine which medication the mother will receive using a stratified randomization design generated with MAPLE software.

The patient will then go back to the operating room when it is her operative time, and we will perform the spinal with bupivacaine, morphine and fentanyl, which is standard at our institution (see standard of care medications below). Once the spinal is confirmed to be adequate, the surgical team will be called in to perform the procedure. Once the baby is delivered and the procedure is completed, we will inject the blinded syringe of medication into the patient's left thigh since she will still be numb from the spinal. When the patient arrives to the PACU, we will assess the 4 variables 1 hour after medication is given in PACU and then between 4-5 hours post-op and at 24 hours post-op (+/- 2 hours). All evaluations will be done in person or by phone call from study coordinator.

If patients are still reporting pruritis that is not controlled, the rescue treatment will be butorphanol 1mg IV q3h, as this is the current regimen at our institution.

Treatment/Therapy
The treatment will consist of a blinded syringe of 1cc clear liquid (blinded to patient and physician – only pharmacist will know what it contains). This injection will be given in the left thigh after the cesarean delivery is completed.

Contents of syringe: (either)
- 1cc 0.9% Sodium Chloride (placebo)
- 1cc 25mg/ml Promethazine (study medication)

Extra studies/procedures required
It is standard of care for all patients for this surgery to have intraoperative 5 lead EKG monitoring. All study patients will have QTc evaluated on the anesthesia monitor. As part of the study, rhythm strips will be printed out and saved in study binder. Any patients with an already prolonged QTc (>500 ms) will be excluded from the study.

Recording data responsibilities
1. Anesthesia attending on OB for the day will consent patient if they agree to the study.
2. Dr. Garvan's team will perform randomization.
3. Study coordinator will be contacted once patient is enrolled.
4. Time 0 will be recorded by resident/attending in the room at the time the medication is given.
5. Study coordinator will contact patient in person or by phone at 1 hour, 4-5 hours , and 24 (+/- 2 hours) hours to assess given variables.

Drugs that will be given as STANDARD OF CARE during the study will be:
1: Bupivacaine 0.75% 1.4-2.0 lT (Spinal anesthetic)
2: Fentanyl 20 mcg IT (Spinal anesthetic)
3: Preservative Free Morphine 100 mcg IT (Spinal anesthetic)
4: Butorphanol 1mg IV every 3 hours (rescue treatment)
5: Nalbuphine 2.5mg IV every 6 hours as needed for itching
6: Ondansetron 4mg IV every 6 hours as needed for nausea
7: Ketorolac 30mg IV once
8: Acetaminophen 975mg by mouth every 6 hours (scheduled)
9: Phenylephrine 100-200mcg as needed every 2 min and phenylephrine infusion 0.1 mcg/kg/min IV titrated to maintain maternal BP within 20% of baseline.
10: Ephedrine 5-10mg IV as needed every 2 min to maintain maternal BP within 20% of baseline, secondary agent to phenylephrine bolus and infusion and/or if maternal HR falls below 70 bpm.
11: Cefazolin 2g IV once before incision
12: Azithromycin 500mg IV once before incision
13: Clonidine 15-30mcg IT (Spinal anesthetic)

If penicillin allergic (given as STANDARD OF CARE):
1: Clindamycin 900mg IV once before incision
2: Gentamicin 1.5mg/kg IV once before incision

Drugs that will be given as part of the study:

1: Intramuscular Promethazine 25mg (25mg/mL)
2: Intramuscular 0.9% Sodium Chloride (placebo, also 1mL)

Table of Study Events

Activity	Time Point	Time Point	Time Point	Time Point
Injection of blinded medication	0			
First Evaluation of variables (Phone call from coordinator)		1 h		
Second Evaluation of variables (Phone call from coordinator)			4-5 h	
Final Evaluation of variables (Phone call from coordinator)				24 h

STATISTICAL METHODS, DATA ANALYSIS, AND INTERPRETATION:

Our plan is to recruit 50 patients for each arm of the study. With 50 patients on placebo and 50 patients on Phenergan, there will be a greater than 80% chance of detecting a significant difference of 20% or more at a two-sided 0.05 significance level. This assumes that severe itching occurs is in 50% of patients and Phenergan reduces this proportion to 20%.

We will use Fisher's exact test to compare groups on severity of itching. We will also use Wilcoxon's rank sum test to compare groups on degree of itching as measured by the ITCHYQUANT. Dr. Garvan, the study biostatistician, will perform all statistical analyses.

DATA STORAGE AND DE-IDENTIFICATION PLANS:

The original, hard-copy signed informed consent forms and rhythm strips will be stored within the locked Anesthesiology research office and will remain with the Principal Investigator for at least 7 years. Data will be entered into an Excel spreadsheet kept on a password-protected and encrypted computer and retained by the Principal Investigator for at least 7 years.

Patients will be de-identified. No names, MRN's, or other identifying information will be stored in the spreadsheet. Pain, itching, sedation and nausea/vomiting will be collected at three intervals by a study coordinator and added to the de-identified spreadsheet. Age group, medical conditions such as diabetes and pre-eclampsia as well as BMI groups, will be used to determine confounders in the data. None of this collected information will be used to identify the patients.

7. **Potential Risks:**

Subjects will be given clear verbal and written instructions to contact Dr. Wendling in the Department of Anesthesiology with questions or concerns regarding their study participation. If a patient experiences an injury that is directly caused by this study, they will receive professional medical care at the University of Florida. No other compensation is offered. Any adverse events will be reported to the

IRB using the standard adverse events reporting website and on continuing reviews (depending upon severity, as defined by the IRB).

1. Sedation (study variable). Promethazine can cause sedation which will be studied.
2. Concern for QT prolongation on the ECG causing cardiac arrhythmias. QTc evaluated on patient monitor, rhythm strip to be printed off and saved in research binder with QTc labeled clearly.
3. Respiratory depression
4. Painful injection site once spinal wears off. Patients will be given the injection while spinal anesthesia is still working to prevent pain during injection.
5. Tissue damage at site of injection
6. There is the risk of loss of confidentiality. The following procedures will be done to maintain confidentiality: written, paper forms will be kept in the locked Anesthesia Research Office. Computerized and de-identified records containing personal health information will be stored on password-protected and encrypted computers.

Routine medications that are provided to patients participating in the study may be provided to you. These are part of normal clinical care. The participant will be responsible for any deductible, co-insurance, or co-payments. Some insurance companies may not cover costs associated with research studies or research-related injuries. If the participant is injured as a direct result of participation in the study, only professional services received from any University of Florida Health Science Center healthcare provider (physicians, physician assistants, nurse practitioners, dentists or psychologists) will be provided without charge. Any other expenses, including Shands hospital expenses, will be billed to the subject's insurance provider or the subject themselves.

Safety Endpoint

During the study, we will log our adverse events. If the incidence for adverse events is greater than expected we will review the study design as a team to decide if we should proceed with the study or stop the study. If we have an increase incidence of serious injection site reactions, we will review whether the medication or placebo is causing the injection site reaction. If any major adverse reactions occur we will have a meeting with the investigators to address if this was an unanticipated or potentially expected event given the expected incidences.

8. **Potential Benefits:**

The potential benefit of this study would be to find a prophylactic treatment for intrathecal opioid pruritus. The patients would undergo minimal risk with an IM injection in attempts to decrease one of the major side effects of intrathecal opioids. The study will benefit future women undergoing cesarean section as we could give intrathecal morphine for post-op pain control with less side effects.

If the hypothesis were rejected, we could also perform future studies to see if the dose of morphine in the spinal could be changed for increase pain control. This study could be also used outside the obstetrics realm and adopted for many different patients receiving intrathecal opioids to decrease post-op pruritus.

9. **Conflict of Interest:**

There are no known conflicts of interest for the staff that will be working on this research proposal.

10. **References:**

1. Slappendel, R., et al. “Itching after Intrathecal Morphine. Incidence and Treatment.” *European Journal of Anaesthesiology*, vol. 17, no. 10, 2000, pp. 616–621., doi:10.1097/00003643-200010000-00004.
2. Penning JP, Samson B, Baxter AD. Reversal of epidural morphine-induced respiratory depression and pruritus with nalbuphine. Can J Anaesth. 1988;35:599-604.
3. Morgan PJ, Mehta S, Kapala DM. Nalbuphine pretreatment in cesarean section patients receiving epidural morphine. Reg Anesth. 1991;16:84-8.
4. Cohen SE, Ratner EF, Kreitzman TR, Archer JH, Mignano LR. Nalbuphine is better than naloxone for treatment of side effects after epidural morphine. Anesth Analg. 1992;75:747-52.
5. Alhashemi JA, Crosby ET, Grodecki W, Duffy PJ, Hull KA, Gallant C. Treatment of intrathecal morphine-induced pruritus following caesarean section. Can J Anaesth. 1997;44(10):1060-5. doi: 10.1007/BF03019227.
6. Eldor J, Fishelev V, Levine S, Guedj P, Dudakova I. Prevention of epidural morphine pruritus by intramuscular promethazine in parturients. Reg Anesth. 1994;19(6):433-4. PMID: 7848959.
7. Horta ML, Morejon LC, da Cruz AW, Dos Santos GR, Welling LC, Terhosrst L, Costa RC, Alam RU. Study of the prophylactic effect of droperidol, alizapride, propofol and promethazine on spinal morphine-induced pruritus. Br J Anaesth. 2006;96(6):796-800. doi: 10.1093/bja/ael072.
8. Vice-O'Con K, Austin PN, Pugh MA. Pharmacologic Methods for Preventing Pruritus in Patients Receiving Intrathecal Opioids for Cesarean Delivery. *AANA J*. 2018;86(1):59-66.
9. Haydek CG, Love E, Mollanazar NK, Rodriguez RV, Lee H, Yosipovitch G, Tharp MD, Hanifin JM, Chen KH, Chen SC. Validation and banding of the ItchyQuant: a self-report itch severity scale. J of Investigative Dermatology. 2017;137:57-61.