Comparison of 0.1 and 0.05mg intrathecal morphine when administered with a multimodal pain regimen for post-cesarean analgesia: a single center, prospective, randomized, single-blinded trial.

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PROTOCOL TITLE:
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PRINCIPAL INVESTIGATOR: Katherine Hatter, MD

1.0 Objectives / Specific Aims

The primary goal of the study is to determine whether or not 0.05 mg of intrathecal morphine is non-inferior to 0.1 mg of intrathecal morphine in providing analgesia for patients undergoing cesarean section at MUSC in the setting of multimodal pain relief strategies.

2.0 Background

There is established efficacy for intrathecal (IT) morphine for postoperative pain control following cesarean section; however, the ideal dose of IT morphine in the setting of multimodal analgesia remains unclear. The American Society of Anesthesiologists recommends the intrathecal administration of preservative-free morphine for patients undergoing cesarean section to provide up to 24 hours of pain relief. [1] The ideal dose of spinal morphine should provide optimum pain control while minimizing the common opioid side effects of pruritus, nausea, vomiting, and in rare cases, respiratory depression. [2]

Several dose-response studies of IT morphine have been performed in the last fifteen years, but these did not include other forms of adjuvant analgesia. A 1999 study compared a wide range of IT morphine dosages (0.0, 0.025, 0.05, 0.075, 0.1, 0.2, 0.3, 0.4, or 0.5 mg) and assessed for pain control as well as side effects. This study concluded that doses of more than 0.1 mg for post-cesarean analgesia did not improve pain control but produced an unfavorable side effect profile. [3] Wong, et al. demonstrated that while IT morphine 0.2mg provided better pain control than lower doses, nausea was increased. [4] Girgin et al. concluded that the dose of 0.1 mg IT morphine produces analgesia comparable with doses as high as 0.4 mg, with significantly less pruritus.[5] Sultan et al. compared low vs high dose IT morphine and demonstrated a greater incidence of side effects in the high dose group.[6]

A recent study by Berger et al. examined IT morphine doses of 0.05mg, 0.1mg, and 0.2mg given in combination with IV ketorolac, a nonsteroidal anti-inflammatory medication, and demonstrated that analgesia was equivalent in all groups with a decrease in pruritus in the 0.05mg group.[7] While this study did include an adjuvant analgesic, it did not incorporate the use of acetaminophen, a medication commonly used for postoperative pain due to its narcotic sparing properties.

The inclusion of both acetaminophen and non-steroidal anti-inflammatory drugs may further reduce the required dose of intrathecal morphine. A recently completed study performed here at MUSC demonstrated that the addition of either intravenous or oral acetaminophen to the standard post-cesarean medication regimen resulted in improved pain control and reduced morphine consumption compared to the no acetaminophen group. However, there was no difference in analgesia between the IV and oral acetaminophen groups. Based on these findings, the postoperative pain management regimen for the first 24 hours following cesarean sections at MUSC includes scheduled administration of oral acetaminophen and IV ketorolac. Preliminary data from 59 patients here at MUSC has revealed that reducing the dose of IT morphine to 0.1mg results in equivalent pain control (time to first rescue dose of IV morphine) compared to IT morphine 0.2mg when given in conjunction with standard of care pain medications. Based on these findings, the current MUSC protocol is to administer 0.1 mg IT morphine as a routine for all cesarean sections.

The primary goal of the study is to determine whether or not 0.05 mg of intrathecal morphine is non-inferior to 0.1 mg of intrathecal morphine in patients undergoing cesarean section at MUSC in the setting of multimodal analgesia by comparing the time to first narcotic rescue dose in the first 24 hours postoperatively. Subjects would receive either 0.1mg or 0.05mg IT morphine during spinal placement. All subjects would receive standard of care pain medications postoperatively. Secondary outcomes will include: a) total opiate consumption at 24 and 48 hours postoperatively; b) time to first ambulation; c) VAS measurements at rest and with ambulation at 24 and 48 hours postoperatively; d) side effects of opiates (nausea, vomiting, pruritus); e) overall patient satisfaction with pain control at 24 and 48 hours postoperatively. We hypothesize that lower doses of intrathecal morphine will provide equivalent postoperative pain control with a reduction in opioid-related side effects. Improved patient quality measures and overall improved patient satisfaction with pain control when added to this institution's current standard of care is expected.

3.0 Intervention to be studied (if applicable)

Preservative-free DURAMORPH (morphine sulfate injection, USP): FDA-approved DURAMORPH is a systemic narcotic analgesic for administration by the intravenous, epidural or intrathecal routes. It is used for the management of pain not responsive to non-narcotic analgesics. DURAMORPH administered epidurally or intrathecally provides pain relief for extended periods without attendant loss of motor, sensory, or sympathetic function.

The rationale for using lower doses of intrathecal morphine is to reduce the side effects of the drug, namely pruritus and nausea, while achieving equivalent pain control.

The control group for the study will receive 0.1mg IT morphine. Study groups will be randomized into 2 groups: 0.1mg IT morphine (control) and 0.05mg IT morphine. All patients will receive the standard of care spinal anesthetic medication. All patients will receive standard of care pain medications postoperatively.

4.0 Study Endpoints (if applicable)

Primary outcome for this study will be time to first narcotic rescue dose in the first 24 hours postoperatively following cesarean delivery.

Secondary outcomes include:

- time to first ambulation
- opiate consumption at 24 and 48 hours
- subjective pain rating using visual analogue scales (VAS) at 24 and 48 hours postoperatively at rest and with ambulation
- presence of opiate side effects (nausea, vomiting, and pruritus)
- overall patient satisfaction with pain control at 24 and 48 hours

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion criteria consist of any parturient 18 years of age or older who is undergoing elective cesarean delivery under spinal anesthesia and is able to consent to the study and participate in the follow-up.

Exclusion criteria include: any known allergy to morphine, general anesthesia, urgent or emergent cases, any bleeding diathesis or other coagulopathy, known G6PD deficiency, any known liver disease, known alcohol abuse or dependence, HELLP syndrome, thrombocytopenia or known platelet dysfunction, history or active gastrointestinal bleeding, acute kidney injury or chronic renal insufficiency, contraindication/refusal to spinal anesthestic, chronic pain, chronic narcotic use, illicit drug use or allergy to any study related medications.

Subjects will neither be selected nor excluded based on ethnicity. The only reason for exclusion based on ethnic category is the inability to speak English. Our interpreter services are limited in time and availability.

6.0 Number of Subjects

236

7.0 Setting

Labor and Delivery floor at MUSC

8.0 Recruitment Methods

Patients will be recruited upon arrival to the Labor and Delivery floor for their elective cesarean section. Patients will be offered participation in the study, if eligible, following the usual pre-anesthetic evaluation by the attending anesthesiologist.

9.0 Consent Process

A study team member will interview and consent a potential participant of the study prior to elective cesarean delivery. Participants will be given time to read the informed consent/HIPAA and have all of their questions answered prior to enrollment. If subjects choose to participate, consent will be documented in writing.

10.0 Study Design / Methods

Project Description: This study will be conducted as a randomized controlled single-blinded clinical trial with patients being randomized to receive either 0.1 or 0.05 mg of IT morphine.

All patients will receive standard of care pain medications postoperatively. Patients will be followed during their hospital stay.

The primary goal of the study is to determine whether or not 0.05 mg of IT morphine is non-inferior to 0.1 mg of IT morphine in patients undergoing cesarean section at MUSC. The primary outcome of interest is time to first opiate rescue dose. Secondary outcomes will include cumulative opiate consumption over time (measured at 12 hour intervals for up to 48 hours), patient reported pain score (on the VAS scale) over time both at rest and with ambulation, occurrence of side effects (nausea, vomiting, or pruritus), and patient satisfaction. Additional information collected on each participant will include maternal age, gestational age, race, weight at delivery, parity, whether or not the patient had a prior C-section, whether or not the patient received intra-operative opiates, whether or not the patient received Tylenol post-operatively, whether or not the patient received Toradol post-operatively, and which opiates were administered post-operatively.

Statistical Analysis Plan and Sample Size Justification:

The primary outcome of interest is time to first rescue opiate dose. The hypothesis of non-inferiority for time to first rescue dose between treatment group will be evaluated using a log-rank testing approach. In a preliminary study based on patients undergoing C-section at MUSC, we found parturients receiving 0.1 mg IT morphine had 1.03 times the hazard of requesting intrathecal morphine compared to the group receiving 0.2 mg of intrathecal morphine and we anticipate a similar change in the hazard when decreasing the dose of intrathecal morphine to 0.05 mg. Additionally, the proportion of parturients requesting no opiates in this study was 5% for the 0.2 mg group and 12% for the 0.1mg group. Using a non-inferiority logrank test, a sample size of 200 subjects (100 per treatment group) provides 80.0% power to detect an equivalence hazard ratio of 1.65 at significance level □ = 0.05 assuming the actual hazard ratio is 1.0, a hazard rate of 0.5 in the 0.1 mg intrathecal morphine group, and that the proportion of subjects censored in each group is approximately 0.07.

Secondary outcomes will include cumulative opiate consumption over time (measured at 12 hour intervals for up to 48 hours), patient reported pains score (on the VAS scale) over time both at rest and with ambulation, occurrence of side effects (nausea, vomiting, or pruritus), and patient satisfaction. The association between treatment group with all categorical outcomes will be evaluated using a chi-square or Fisher's exact test where appropriate. Associations between treatment group and cumulative opiate consumption and pain score over time (either at rest or with ambulation) will be examined using a series of linear mixed models. All mixed models will include fixed effects for treatment group, time, and the treatment group by time interaction and a random subject effect to account for repeated measures collected on the same subject. Various correlation structures will considered, and the final structure will be selected based on the model

Akaike information criterion (AIC). Additionally, Harrell's rule of thumb states that 10 subjects per covariate are required to avoid overfitting.[8] Thus, we will also include up to 7 additional covariates in order to account for potential confounders associated with opiate consumption or patient reported pain over time. All analyses will be conducted in SAS v. 9.4 (SAS Institute, Cary NC).

We plan to enroll 118 subjects per group (236 total) to allow for 15% attrition rate.

11.0 Data Management

The following data will be collected from the subjects medical record or interview: time to first narcotic rescue dose, time to ambulation, subjective pain rating using visual analogue scales (VAS) at 24 and 48 hours postoperatively at rest and with ambulation, opiate consumption at 12, 36, and 48 hours, overall patient satisfaction with pain control at 24 and 48 hours, administration of Tylenol and Toradol, and presence of opiate side effects (nausea, vomiting, and pruritus).

Upon enrollment, subjects will be assigned a randomized numerical identifier for the remainder of the study. This number will be used to label charts and paperwork associated with the subject. An electronic enrollment log will link patient name and MRN with her study ID number. All paper information will be kept in a locked cabinet in a locked office. All electronic data will be kept on MUSC's password protected server.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects (if applicable)

Data and safety monitoring will be performed by the research study committee in the Department of Anesthesia and Perioperative Medicine on a annually basis. The committee is comprised of several attending anesthesiologists, the chairman of anesthesiology, and an emeritus dean of medicine. Any adverse events will be reported to MUSC's IRB per protocol and will be evaluated by the committee. The primary endpoint of this study is to determine the ideal dose of intrathecal morphine for post cesarean pain.

13.0 Withdrawal of Subjects (if applicable)

Circumstances under which subjects will be withdrawn from the research without their consent include conversion to general anesthesia due to failed spinal or fetal/maternal distress or unrecognized allergy/intolerance to morphine, ketorolac, or acetaminophen.
If patients voluntarily withdraw from the research study, they will receive our institutional standard of care for perioperative pain management.

14.0 Risks to Subjects

The risk to the subject, namely suboptimal pain control requiring additional dosing of IV morphine, does not pose long term negative consequences. Patients will receive IV pain medications as needed to achieve adequate pain relief.

Morphine is an FDA approved medication; however, too much morphine can lead to sedation and respiratory depression. Patients will be monitored with continuous pulse oximetry while on the ward.

Allergic reaction to morphine is possible. Any reaction to the study drug will be treated per MUSC protocol for drug reactions and the medication will be discontinued. Any potential participant with an allergy to morphine will be excluded from the study.

If any of the listed skin reactions (please see E1) occur the study drug will be stopped immediately.

Risks include allergic reaction, respiratory depression, pruritus, nausea, vomiting, constipation, and skin reactions.

Symptoms of allergic reaction to morphine may include: hives, difficulty breathing, and swelling of your face, lips, tongue, or throat.

There is a risk of loss of confidentiality.

Alternative: Patients may choose to not participate or withdraw from the study at any time.

15.0 Potential Benefits to Subjects or Others

Benefits of this research include a potential reduction in side effects in the postoperative period. We anticipate that a reduction in pruritus will result in improved patient satisfaction as well as decreased administration of medications to treat pruritus. A reduction in postoperative nausea would also be beneficial to the patient as this is generally a major contributor to patient dissatisfaction.

Establishing the optimal dose of IT morphine is relevant in order to improve postoperative pain control following abdominal surgery. All patients will receive the standard of care at MUSC, which includes multimodal pain regimens. Patients receiving lower dosages of IT morphine may benefit from reduced nausea, vomiting, and/or pruritus.

16.0 References

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