PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	Optimal Dose of Intrathecal Morphine for Postoperative Analgesia after Cesarean Delivery
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B1. PURPOSE OF PROTOCOL

To investigate the optimal dose of intrathecal morphine for postoperative pain control after cesarean delivery in the setting of postoperative multimodal analgesia. To determine if ultralow and low doses of intrathecal morphine are non-inferior to high dose of morphine for post cesarean pain control.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Cesarean delivery is the most common surgical procedure in the United States, with approximately 1.2 million cesarean deliveries performed in 2019 (1). Intrathecal (IT) morphine is considered the choice medication for postoperative pain control for cesarean delivery (CD) for its prolonged analgesic effects. However, this medication can cause significant side effects such as nausea/vomiting and pruritis (itching).

Historically, large doses of spinal morphine (> 500 mcg) were used but, more recently, most institutions have transitioned to lower doses because of the high frequency of side effects. This transition has been guided by many studies that show comparable pain relief with varying doses. In a classic, but relatively small study, Palmer et al, investigated the quality of analgesia and incidence/severity of side effects of for post-cesarean analgesia (measured by cumulative intravenous PCA-administered morphine). The doses of IT morphine ranging from 0 to 500 mcg, and they found that doses of 100 mcg or more were found to produce analgesia comparable with 500 mcg, but with an increase in side effects among the higher doses (2). Similarly, Girgin et al, found IT morphine dose of 100 mcg provided comparable analgesia to 400 mcg, but with less pruritis (3).

Thus, most centers now use a lower range of doses (≤ 250 mcg) for spinal morphine. Some studies examining morphine doses in this lower range suggest pain relief may be more effective and longer lasting when a higher dose is used. A retrospective chart review performed by Wong et al, found that IT morphine 200 mcg provided better analgesia compared to 100 mcg, but with higher incidence of nausea (4). A meta-analysis performed by Sultan et al, found significant prolongation of analgesia with high dose IT morphine (>100-250 mcg) group as compared to low dose IT morphine (50-100 mcg) group. This meta-analysis also found a higher incidence of side effects in the high dose group (5).

Since the publication of these studies, the standard practice has changed. The current expectation of pain management consists of 'multimodal' strategies that include standing orders for non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. Therefore, the aforementioned studies may not be applicable to today's practice, as the use of NSAIDs and acetaminophen postoperatively may further decrease the optimal dose of IT morphine. This was noted in a recent study by Berger et al, which showed that 50mcg of IT morphine, with the addition of postoperative IV ketorolac, produces analgesia similar to 150mcg (6).

In conclusion, there is a gap in knowledge in defining the optimal dose of spinal morphine for pain relief after cesarean delivery when using multimodal analgesia. Our goal is to evaluate the effectiveness and duration of pain relief when using low doses in combination with multimodal pain relief strategies.

References

1. CDC, National Vital Statistics Reports, Vol. 70, No. 2, March 23, 2021
2. Palmer CM, Emerson S, Volgoropolous D, Alves D. Dose– response relationship of intrathecal morphine for postcesarean analgesia. Anesthesiology 1999;90:437–44.
3. Girgin NK. Intrathecal morphine in anesthesia for cesarean delivery: dose–response relationship for combinations of low-dose intrathecal morphine and spinal bupivacaine. J Clin Anesth 2008;20:180–5.
4. Wong JY, Carvalho B, Riley ET. Intrathecal morphine 100 and 200 lg for post-cesarean delivery analgesia: a trade-off between analgesic efficacy and side effects. Int J Obstet Anesth 2013;22:36–41.
5. Sultan P, Halpern SH, Pushpanathan E, Patel S, Carvalho B. The effect of intrathecal morphine dose on outcomes after elective cesarean delivery: a meta-analysis. Anesth Analg 2016;124:154–64.
6. Berger JS, Gonzalez A, Hopkins A, Alshaeri T, Jeon D, Wang S, Amdur RL, Smiley R. Dose-response of intrathecal morphine when administered with intravenous ketorolac for post-cesarean analgesia: a two-center, prospective, randomized, blinded trial. Int J Obstet Anesth. 2016 Dec;28:3-11.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Study Design
Prospective, randomized, double-blind, controlled trial.

Endpoints:
Primary outcome: Identify duration of analgesia defined as time to patient request for first dose of oral rescue pain medicine (up to 24 hours postopertatively).

Secondary outcomes: pain scores over 24 hours, Quality of Recovery Score at 24 hours after delivery, incidence of side effects (requiring treatment for side effects), need for rescue PCA for severe pain, need for rescue regional blocks for severe pain, temperature, and respiratory depression.

Brief Study Protocol:
Patients will be randomly assigned to receive either intrathecal morphine 50 mcg, 150 mcg, or 250 mcg based on a pre-assigned randomization sequence. The assignment for each patient will be kept in the research pharmacy. After obtaining written informed consent, research pharmacy will provide the team with appropriate syringe for intrathecal administration. The patient, clinicians and the study investigators will all be blinded to the study medication.

Standard care:
All patients will receive standard of care for cesarean delivery and routine nursing care. This includes: preoperative intravenous catheter placement with preoperative IV fluid, standard American Society of Anesthesiologists monitoring, and neuraxial anesthesia placement (either spinal or combined spinal epidural) in sterile fashion. Each patient will receive standard cesarean induction dose of intrathecal medication consisting of 1.5ml of 0.75% hyperbaric bupivacaine, fentanyl 25 mcg. At end of surgery, all patients will receive standard dose of ketorolac 30 mg IV and acetaminophen 1 gm IV and continue with redosing every 6 and 8 hours (respectively) for 24 hours. On arrival to PACU, all patients will receive standard nursing care with standard monitoring of side effects. On discharge from PACU, patients will be transferred to postpartum floor and receive standard nursing care and monitoring.

Over the following 24 hours, the patient will receive all standard post-cesarean care.
For treatment of breakthrough pain, medications will provided be per standard care: oxycodone 5-10 mg PO every four hours PRN for pain. If the patient is not comfortable after receiving oral oxycodone they will be assessed by an anesthesia provider for either regional nerve block or additional opioids, as a one-time dose or by patient controlled analgesia (PCA).

For treatment for side effects, medications will provided be per standard care: ondansetron 4mg IV as first-line for nausea/vomiting, promethazine 6.25 mg IV or Haloperidol 0.5-1mg IV for refractory nausea/vomiting. Naloxone 0.04 mg IV for refractory pruritus.

Measurements:
Study measurements will all be recorded by a blinded investigator.

Patients will be asked to score their pain on a Visual Analog Scale (10 cm, unmarked line) on arrival to PACU, 2 hours postoperatively, and 24 hours postoperatively. At 24 hours, patients will be asked to complete Quality of Recovery Score following Cesarean Delivery Questionnaire (ObsQoR-11).

Time to first request for additional pain medications will be recorded. Pain scores and side effects will be recorded from standard nursing assessments during the 24-hour study period.

B. Statistical Considerations

a. ***Sample Size Justification:***

The study will be powered for non-inferiority of the duration with 80% power and assuming a median difference of 4 hours between the dose groups, we will need 20 patients per group. With the ~20% drop-out rate, this should be increased to 24 patients per group.

b. ***Data Analysis:*** .

The primary outcome will be the time to patient request for first dose of oral rescue pain medicine using a non-inferiority test.

We will compare the duration of analgesia among patients who have side effects requiring treatment to determine whether the treatment of side effects has an effect on pain relief. If this is found to be significant, then an analysis of duration stratified by side effect will be performed. Additional outcomes will be compared using ANOVA, Kruskal-Wallis, or Fisher's exact test, as appropriate. Comparisons between two groups will be performed using t-test or Mann-Whitney test, as appropriate. The Shapiro-Wilk test will be used to assess normality of the data.

Significance will be determined at the $P \leq 0.05$ level.

C. Subject Selection

All patients will be selected from the schedule or add-on list of cesarean deliveries at BIDMC. All patients will meet inclusion and exclusion criteria.

Inclusion criteria:

- Healthy women (ASA 2)
- Between 18 and 45 years old
- Singleton term pregnancies
- Planned neuraxial anesthesia

Exclusion criteria:

- Refusal to participate
- Known allergy or contraindication to any medication used in the study
- Significant medical or obstetrical disease (ASA ≥ 3)
- Opioid use disorder
- Chronic pain syndrome
- Daily or near daily opioid use within last 3 weeks.

B4. POSSIBLE BENEFITS

Unknown if inclusion in the study will provide patient any benefit as all patients will receive intrathecal morphine, regardless of participation in this study. If we determine best dose, future patients will benefit from knowledge gained.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Patient would be receiving intrathecal morphine regardless of participation in this study. Depending on the dose received, the patient may experience more or less side effects or more or less pain. However, all patients will be provided additional pain medications and treatment for side effects. It is unknown if smaller dose of morphine will reduce the duration of pain control and significantly greater need for treatment of side effects.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

All patients will be identified from the schedule and add-on list of cesarean deliveries at BIDMC. The pateints will be approached by a study investigator who will determine the patient's willingness to participate and if the patient may meet inclusion and exclusion criteria. The investigator will present the study to the patient and perform informed consent for enrollment in the study.

Consent

The study investigator will obtain written informed consent from the potential subject in the preoperative holding area. This is a secure location that is currently used for all medical conversations with patients, including informed consent. The patient's support person(s) (e.g. spouse, parent, etc.) may remain for the informed consent procedure.

Subject Protection

This study does not include vulnerable populations.

B7. STUDY LOCATION

Privacy

All conversations will be had in the secured area currently used for private medical conversations. No information will be shared outside of the study personnel and BIDMC. Patient information will extracted from the medical record and entered into a Redcap database. Any paper notes will be destroyed in a HIPAA compliant fashion at the earliest opportunity.

Physical Setting

All conversations and consent discussions will be help in the preoperative area designed for this type of interaction. The patient will be cared for on the labor and delivery unit for the cesarean delivery, and on the postpartum unit for their recovery. These are the typical locations for these women, whether participating in a study or not.

B8. DATA SECURITY

Initial study documents including consent and enrollment documentation will be stored in the Obstetric Anesthesia office in a secured location, accessible to research investigators. Study data will be collected and managed using REDCap, with any notes recorded on paper being destroyed in a HIPAA compliant manner. All study records will be maintained until three years after study publication, and will be destroyed after that.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☐ No

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☐ No

B10 Dissemination of Research Results

Please explain whether you will be able to thank subjects and provide research results and, if so, how this will be accomplished. If you do not think this is feasible, appropriate or applicable to this research, please specify why.

Patients will be thanked at time of enrollment, however research results will not be routinely distributed to the patients at completion of the study. If a patient specifically requests their individual results or the aggregated results, this will be permitted on an individual basis.