Intrathecal Morphine vs. Intrathecal Hydromorphone for Analgesia Following Cesarean Delivery

NCT# 02789410

December 21, 2015

DETAILED PROTOCOL **12/21/15**

Principal/Overall Investigators
Hans P. Sviggum, MD, Emily Sharpe, MD

Protocol Title
Intrathecal morphine versus intrathecal hydromorphone for analgesia following cesarean delivery

Background and Significance
Spinal anesthesia is the most common anesthetic technique used for Cesarean delivery in the United States and across the world (1). Intrathecal opioids are administered with a local anesthetic during spinal anesthesia post-Cesarean delivery analgesia. The effectiveness of intrathecal morphine for post-Cesarean pain control is well established (2-4), and the use of intrathecal hydromorphone in this patient population is growing (5-8). No prospective studies have been conducted to specifically compare the efficacy of intrathecal morphine versus hydromorphone for post-Cesarean analgesia.

After intrathecal administration, opioid drug disposition depends on the lipid solubility of the individual drug. Because of its hydrophilic nature, CSF concentrations of morphine decline more slowly than similar doses of lipophilic drugs. This accounts for more rostral spread, greater dermatomal analgesia, and longer duration of action when compared to highly lipophilic opioids like fentanyl and sufentanil. When used for post-cesarean analgesia, intrathecal morphine has a duration of action between 14-36 hours (9) with wide variation between individual patients. While hydromorphone is similar chemically to morphine, it is more lipid soluble. This decreases its spread within the intrathecal space and enhances its penetration into the dorsal horn of the spinal cord where interactions with opioid receptors occur. These differences between the two medications may influence their duration of action. Theoretically, this would reduce the duration of action of intrathecal hydromorphone when compared with intrathecal morphine. Retrospective studies have shown that the analgesic benefit for intrathecal hydromorphone appears to extend at least 12 hours after cesarean delivery and may extend up to 24 hours (6,8).

Although effective in reducing pain, intrathecal opioids are associated with side effects including pruritus, nausea, and respiratory depression. A meta-analysis reviewing twenty-eight studies which investigated intrathecal morphine versus placebo demonstrated moderate increases in the incidences of pruritus, nausea and vomiting (10). In fact the incidence of nausea with IT morphine has been reported to be nearly 33% (2, 11). The differences in pharmacokinetics between morphine and hydromorphone may also create differences in side effect profiles. Some studies have found that hydromorphone causes less nausea and pruritus than morphine (4), while others have not (5). Although opioid-induced respiratory depression is a rare event, studies evaluating intrathecal hydromorphone for post-Cesarean delivery pain have not reported any cases of respiratory depression (5-6).

In this study, we aim to compare the duration of analgesia of intrathecal morphine vs. hydromorphone for analgesia after cesarean delivery. Secondarily, we will compare the side effects of each drug, including nausea and pruritus. To achieve the goals of this study, it is important to study equipotent doses of these medications. Previous work by our group found that the effective dose for postoperative analgesia in 90% of patients (ED_{90}) is 75 micrograms for intrathecal hydromorphone and 150 micrograms for intrathecal morphine (8). However, we do not know if these two equipotent medication doses provide a similar duration of analgesia.

We hypothesize that 150 mcg of intrathecal morphine will result in a longer duration of analgesia when compared to 75 micrograms of intrathecal hydromorphone. Additionally, we hypothesize that there will be more pruritus in the intrathecal hydromorphone group early after surgery, and no difference in side effects at 24 hours after surgery.

<u>Specific Aims</u>

Specific Aim 1: To determine if there is a difference in effective analgesia at 24 hours after cesarean delivery between patients receiving 150 mcg intrathecal morphine versus 75 mcg intrathecal hydromorphone.

Specific Aim 2: To determine if there is a difference in the frequency of moderate/severe nausea or pruritus between 150 mcg intrathecal morphine versus 75 mcg intrathecal hydromorphone at any time point following cesarean delivery.

Study Hypothesis

We hypothesize that 150 mcg of intrathecal morphine will result in a longer duration of analgesia when compared to 75 micrograms of intrathecal hydromorphone. Additionally, we hypothesize that there will be more pruritus in the intrathecal hydromorphone group 6 hours after surgery, with no differences in side effects at 24 hours after surgery.

Methods

Design: Single Center, Double-blinded, Randomized control trial

Subject Selection

To qualify for the study, subjects must meet the following inclusion/exclusion criteria:

Inclusion:

1. ASA physical status II-III women presenting for elective cesarean delivery with or without tubal ligation
2. Singleton or twin gestation at term (37-42 weeks)
3. Desire to have a spinal anesthesia technique for cesarean delivery

Exclusion:

1. Any contraindication to the administration of a spinal technique for anesthesia
2. History of intolerance or adverse reaction to opioid medications
3. Chronic pain syndrome or current opioid use >30 oral morphine equivalents/day
4. Allergy or intolerance to acetaminophen, ketorolac, ibuprofen, or oxycodone
5. Current BMI > 50
6. Concomitant procedures (e.g. ovarian cystectomy)

Potential subjects will consist of parturients who present for elective cesarean delivery at the Family Birthing Unit at Methodist Hospital, Mayo Clinic. Subjects will be approached following the verbal communication and approval of their obstetric provider. Recruitment will ideally occur either at the patient's last obstetric visit prior to delivery or by telephone call 2-7 days prior to her cesarean delivery. Recruitment may also occur on the morning of the cesarean delivery in select cases. Only licensed physician investigators will recruit subjects. No remuneration will be provided. All efforts will be made to enroll participants regardless of ethnic heritage, including the use of interpreters. No passive recruitment methods (newspapers, advertisements, or flyers) will be used.

Subject Enrollment

Informed consent will be obtained by one of the licensed physician investigators either at the earliest opportunity when the patient arrives in the family birth center.

Subjects unable to give consent themselves will not be approached for participation.

In order to obtain 130 completed subjects for our primary analysis, our proposed target accrual is 150 subjects. These subjects will be randomized to receive either intrathecal morphine (150 mcg) or hydromorphone (75 mcg) as part of their spinal anesthesia. Up to 200 subjects may be screened in ourder to reach our target accrual numbers. The standard technique for administration of spinal anesthesia will not be

altered. The randomization process will occur through the use of a computer generated randomization scheme with allocation concealment in numbered opaque envelopes carried out by a blinded observer.

Study Procedures
Following informed consent and randomization, an anesthesia provider not involved in postoperative assessment will prepare the opioid medication for intrathecal injection.

Upon request for anesthesia, subjects will have a spinal anesthetic placed in the usual fashion at the L3-4 or L4-5 interspace. Spinal anesthesia will consist of the medication regimen currently used at our institution for cesarean delivery anesthesia: 1.6 mL of 0.75% bupivacaine with dextrose, 15 mcg of fentanyl, and either morphine or hydromorphone according to study protocol and randomization. Normal saline will be added to the syringe containing morphine or hydromorphone to make this volume 1 mL. This will then be added to the bupivacaine/fentanyl mixture prior to administration. Time of spinal injection will be noted as time "0". Strict aseptic techniques, as in current clinical practice, will be utilized throughout each procedure; these include the anesthesiologists wearing hat, mask, and sterile gloves during spinal placement.

All patients will have a phenylephrine infusion that is started at 0.5 mcg/kg/min at the time of administration of spinal anesthesia, which is our usual current practice. Further intraoperative blood pressure management will be left to the discretion of the anesthesia provider with the goal of maintaining the patient's blood pressure at 80-100% of normal. Each patient will receive 0.1 mg granisetron after delivery of the baby. All patients will be treated with our institution's standard "Obstetric Neuraxial Analgesia" order set (MC1156-670rev0514). This allows for standard monitoring of respiratory rate, oxygenation, and sedation with appropriate treatment as needed. Nausea and pruritus will be treated as needed by current protocol. All patients will also be treated with our institution's standard post-cesarean order set (MC2222-04). This order set provides scheduled acetaminophen 1000mg orally every 6 hours and ketorolac 15mg intravenously every hour for three doses, which is then replaced with ibuprofen 600mg orally.

Data Collection: All data will be collected prospectively by patient interview at 6, 12, 18, 24, 30, and 36 hours after spinal administration (see data collection sheet). At each time point, patients will rate the following:

1) NRS score for pain (0-10) at rest
2) NRS score for pain (0-10) with movement
3) Highest pain NRS (0-10) in previous 6 hours
4) Nausea – 0 = none, 1 = mild, 2 = moderate, 3 = severe
5) Pruritus – 0 = none, 1 = mild, 2 = moderate, 3 = severe
6) Overall satisfaction with analgesia – 0 = satisfied, 1 = somewhat satisfied, 2 = neutral, 3 = somewhat dissatisfied, 4 = dissatisfied
7) Sedation score (Richmond Agitation Sedation Scale)
8) Any instances of respiratory depression (#)

Other data collected from patient electronic records will include:
1) Total opioid consumption at 24 and 36 hours of intrathecal opiate administration
2) Total non-opioid analgesic consumption at 24 and 36 hours of intrathecal opiate administration
3) Medical treatment(s) for nausea or pruritus at 24 and 36 hours of intrathecal opioid administration
4) Maternal demographics and fetal characteristics (birthweight, Apgar scores)

Primary Outcome: NRS score for pain (0-10) with movement 24 hours after spinal administration

Secondary Outcomes:
1) Severity of any opioid-related complication at each time point

a) Pruritus
b) Nausea
c) Sedation (Using Richmond Agitation Sedation Scale)

2) Total opioid consumption (in oral morphine equivalents) at 24 and 36 hours of intrathecal opiate administration
3) NRS score for pain at rest 6, 12, 18, 30, 36 hours after spinal administration
4) Number of treatments for nausea and pruritus at 24 and 36 hours of intrathecal opiate administration

Early end points:

1) Change in fetal or maternal health mandating the use of other anesthetic techniques
2) Inability to perform the spinal technique
3) Withdrawal of subject consent at any time
4) Surgical complications resulting in the need for additional surgical procedures

Subject Costs:
There will be no additional costs to the patient as a result of participation in this study. The costs of routine labor and delivery analgesia and anesthetic care will be the responsibility of the patient and their insurance provider.

Statistical Analysis

A sample size of n=65 per group will provide 90% power (two-tailed, alpha=0.05) to detect a difference between groups of 1.0 unit for NRS pain scores at 24 hours. NRS scores for pain, nausea, and pruritus will be analyzed by rank sum test. Maternal and fetal demographics will be tested by ANOVA (continuous data) or chi-square (categorical data) as appropriate. Statistical significance will be assumed when $P < 0.05$. The primary analyses will be performed according to an intention-to-treat principle and will include data from all randomized subjects. Compliance with trial procedures, dropouts, and reasons for subject withdrawal will be tracked throughout the study. Adverse events will be tabulated, with severity and resultant treatment recorded. For each adverse event, the treatment groups will be compared using Fisher's exact test.

Risks and Discomforts
We will be utilizing doses of hydromorphone and morphine that we previously identified as an effective dose for postoperative analgesia in 90% of patients (ED90). However, any and every patient who experiences pain after Cesarean delivery will be treated with standard analgesic medications titrated to patient comfort, regardless of type of intrathecal opioid used.

Hypotension is one of the most common sequelae from spinal anesthesia techniques. Intravascular volume expansion, avoidance of aortocaval compression, and standardized vasopressor treatment will be immediately available and utilized if needed. The risk of hypotension will not be increased due to the randomization of study medications.

Approximately 10-40% of the time, nausea may occur. If nausea occurs, it will be treated and managed according to usual measures. Approximately 10-70% of the time, pruritus may occur. If pruritus occurs, it will be treated and managed according to usual measures.

The risk of a post dural puncture headache (PDPH) exists for spinal techniques. The risk is approximately 1% in an obstetric population with a 25 gauge Whitacre needle, and will not be increased by the administration of study medications. If a PDPH occurs, various methods are available for treatment and will be discussed with the patient.

Uncommon (less than 1%) but possible sequelae of all techniques discussed include failure to obtain anesthesia, incomplete anesthesia, and need to repeat the spinal anesthetic (for anesthesia only, not for the purposes of the study). The use of the study medications will not increase these risks.

Rare (less than 0.1%) but possible sequelae include infection, epidural or spinal hematomas, and nerve injury. The use of the study medications will not increase these risks.

Potential Benefits
Patients may experience improved pain control with fewer opioid related side effects. The information from this study may benefit other patients undergoing neuraxial anesthesia for Cesarean delivery.

Monitoring and Quality Assurance
Assurance of safety and tolerability:
Following continuous care during the Cesarean delivery, all patients will have a scheduled visit at 6 hours, 12 hours, 18 hours, 24 hours, 30 hours, and 36 hours after intrathecal injection to evaluate the efficacy of analgesia. As noted, numerical rating scale pain scores, satisfaction, and opioid side effects will be recorded by a blinded observer who will be able to immediately notify a physician investigator if problems or concerns are noted. Unscheduled interventions for alterations in maternal or fetal condition will be dictated by the obstetric, nursing, and anesthetic providers in care of the patient; appropriate treatments will be at the discretion of the treating provider. All scheduled and unscheduled interventions will be recorded. Due to the short duration of this study, there are no plans for interim analyses; however, should it appear to any investigator or obstetric, nursing or other anesthetic provider that adverse events or treatment failures are occurring; such an analysis will be conducted. A patient may withdraw from the study at any time.

Serious Adverse Experiences:
Any serious or unexpected adverse experiences (AE), whether or not considered to be related to the study, shall be reported immediately to the Research Compliance Office at Mayo Clinic, followed by a letter summarizing the event within 5 business days. The event will also be reported within 2 working days to the Director of Obstetric Anesthesia, Katie Arendt and to the Clinical Practice Chair for Rochester Methodist Hospital, Jim Hebl. In addition, the Director of Labor and Delivery and the Director of Labor and Delivery Nursing will be contacted within 5 working days. Any and all of these individuals may halt the further collection of this study.

All adverse experiences will be recorded and evaluated for causality with the techniques used in this study. The method of causality will be determined by the above mentioned individuals based on sufficient information for evaluation including, but not limited to: A reasonable temporal relationship between the AE and the techniques, an AE that is not a common, expected sequelae of the techniques, an AE that cannot be adequately explained by other documented circumstances of the case.

References

1) Bucklin BA, Hawkins JL, Anderson JR, Ullrich FA. Obstetric anesthesai workforce survey: twenty year update. Anesthesiology 2005;103(3):645-53

2) Gehline M , Tryba M. Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. *Anaesthesia* 2009;64:643-51
3) Palmer CM, Emerson S, Volgoropolous D, Alves D. Dose-response relationship of intrathecal morphine for postcesarean analgesia. Anesthesiology 1999;90;437-44
4) Terajima K, Onodera H, Kobayashi M, et al. Efficacy of intrathecal morphine of analgesia following elective cesarean section: comparison with previous delivery. J Nippon Med School 2003;70:327-33
5) Beatty NC, Arendt KW, Niesen AD, Witwer ED, Jacob AK. Analgesia after cesarean delivery: a retrospective comparison of intrathecal hydromorphone and morphine. J Clin Anesth 2013;25:379-83
6) Rauch E. Intrathecal hydromorphone for postoperative analgesia after cesarean delivery: a retrospective study. AANA J 2012;80:S25-32
7) Rauch E. Intrathecal hydromorphone for cesarean delivery: in search of postoperative pain management: a case report. AANA J 2011;79:427-32
8) Sviggum HP, et al. In submission.

9) Carvalho B, Butwick A. Postoperative analgesia: epidural and spinal techniques, Chestnut's Obstetric Anesthesia, 5th edition. Edited by Chestnut DH, Wong CA, Tsen LC, Ngan Kee WD, Beilin Y, Mhyre JM. Philadelphia, Elsevier Saunders, 2014, pp 621-61
10) Gehling M, Tryba M. Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. Anaesthesia 2009;64:643-51
11) Nortcliffe SA, Shah J, Buggy DJ. Prevention of postoperative nausea and vomiting after spinal morphine for Caesarean section: comparison of cyclizine, dexamethasone and placebo. Br J Anaesth 2003;90:665-70