Comparison of Intrathecal Hydromorphone and Intrathecal Morphine for Postoperative Analgesia After Cesarean Delivery

PI: Dr. Yaakov Beilin

NCT02096003

Document Date: July 20, 2012

Mount Sinai / MSSM / MOUNT SINAI SCHOOL OF MEDICINE	Protocol Title:	
	Principal Investigator:	
	Primary Contact Name/Contact Info	
	Date Revised:	
	Study Number:	

MSSM Protocol Template HRP-503a

Instructions:

1. *Prepare a document with the following sections. Note that, depending on the nature of your research, certain sections below may not be applicable. Indicate N/A as appropriate, explaining where possible.*
2. *For any items described in the sponsor's protocol, grant application or other source documents submitted with the application, you may reference the title and page numbers of these documents rather than cutting and pasting into this document.* ***Do NOT refer to any derived documents, such as the Sample Consent document, or other internal documents required with the submission.***
3. *If you reference page numbers, attach those pages to this protocol.*
4. *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*

Brief Summary of Research (250-400 words):

The use of intrathecal opioids for analgesia in the setting of cesarean section has become standard obstetric anesthesia practice. Currently, two opioids are commonly used. These opioids are fentanyl and morphine (Duramorph). Intrathecal opioids are an excellent source of analgesia and act to reduce the stress response to surgery. Currently, most obstetric anesthesiologists use intrathecal morphine for analgesia after cesarean delivery. Morphine provides excellent analgesia for cesarean section. However, use of this medication is associated with side effects such as pruritus and nausea and vomiting.

Recently, there was a shortage of preservative free morphine. As a result, alternative forms of analgesia had to be utilized for multiple operations, including cesarean delivery. Multiple obstetric anesthesia groups began to use intrathecal hydromorphone for cesarean delivery when morphine was unavailable. Unfortunately, there was very little data regarding its use for cesarean section at that time. As groups began to use hydromorphone, retrospective data became available that demonstrated its safety and efficacy for use during cesarean section.

In order to fully elucidate the analgesic and side effect properties of hydromorphone for cesarean delivery, a prospective randomized, double blind study comparing morphine and hydromorphone is necessary. We need to understand whether hydromorphone is as effective as morphine for analgesia after cesarean section, and whether it is associated with fewer or more side effects. The results of the study will allow providers to make educated decisions to better care for their patient.

1) Objectives

The purpose of this study is to determine whether there is a difference in analgesic effect of intrathecal morphine and hydromorphone for cesarean section.

2) Background

Opioids are often administered intrathecally for cesarean section for post-operative analgesia. Opioids act in the substantia gelatinosa of the dorsal horn of the spinal cord. When activated, these receptors inhibit the release of excitatory neurotransmitters within the spinal cord. The most important factor to consider when administering intrathecal opioids is the lipid solubility.

Lipophilic opioids, such as fentanyl, enter the spinal cord rapidly, quickly diffuse across the dura and into the epidural fat and are rapidly cleared into the systemic circulation. Due to the rapid distribution, lipophilic opioids have limited spread within the cerebrospinal fluid (CSF). As a result of these features, lipophilic opioids result in a rapid onset and short duration of action. Fentanyl, for example, has an onset of action of 5-10 minutes and duration of 2-4 hours.

Hydrophilic drugs, such as morphine, travel slowly within the spinal cord, and have slower clearance. Thus, hydrophilic opioids have a slower onset, longer duration of action, and a higher degree of cephalad spread. Morphine is the prototypical mu-opioid receptor agonist and is the most hydrophilic of the frequently used intrathecal opioids. Intrathecal morphine has a relatively slow onset (30-60 min) and lasts approximately 24 hours. Morphine has a small intrathecal volume of distribution and slower clearance than lipophilic opioids. Morphine metabolism results in active metabolites. Morphine-6-glucuronide (M6G) and Morphine-3-glucuronide (M3G) are the primary active metabolites. M6G is thought to be responsible for analgesic properties of morphine, but also contributes to the side effect of respiratory depression. The intrathecal potency of M6G is approximately 10-45 times greater than that of morphine. (1)

Hydromorphone, another hydrophilic opioid, is a semi-synthetic ketone of morphine. Hydromorphone is slightly more lipophilic than morphine and therefore has a faster onset of action and shorter duration of action. Hydromorphone is approximately five times more potent than morphine when administered intrathecally. Furthermore, hydromorphone appears to have a more favorable side

effect, with possibly less pruritus and nausea. This is perhaps due to lack of active metabolites or because of its smaller volume of distribution.
Currently, most obstetric anesthesiologists use intrathecal morphine for analgesia after cesarean delivery. Based on the pharmacokinetics of morphine and hydromorphone, it would appear that the use of intrathecal hydromorphone for cesarean delivery may result in a similar analgesic profile with fewer side effects. A retrospective study by Rauch (2013) sought to compare the analgesic and side effect profile of intrathecal hydromorphone with local anesthetic vs. intrathecal fentanyl with local anesthetic vs. local anesthetic alone for cesarean section. Pain scores were gathered retrospectively from self-report in response to a nurse's questions. In this study, hydromorphone significantly reduced pain scores in the 0-4 hour range and the 24 hour range as compared to local anesthetic alone or in conjunction with fentanyl. This is the only study in the literature that investigated that role of intrathecal hydromorphone and showed that it provides effective analgesia for cesarean section. There was also a study by Halpern et al. (1996) that compared epidural hydromorphone with epidural morphine for cesarean section. This study found no difference in analgesic effect between the two groups. The Halpern study did identify an earlier peak of pruritus in the hydromorphone group and a later peak in the morphine group. There are, however, no studies that compared intrathecal hydromorphone with intrathecal morphine for cesarean delivery. In order to further characterize the analgesic and side effect profile of intrathecal hydromorphone and determine its future role in obstetric anesthesia, a prospective randomized double blind trial is necessary.

3) Setting of the Human Research

This study will take place at the Mt Sinai Hospital Labor and Delivery Floor. Patients eligible for the trial will be approached by a member of the investigating team after admission to the labor and delivery unit for primary elective cesarean section. These patients will be informed about the trial and consent will be obtained. If the patient does not wish to take place in the trial, she will receive standard anesthetic care.

4) Resources Available to Conduct the Human Research

The study will involve 50 patients scheduled for primary elective cesarean section. The Mt Sinai labor and delivery unit is a very busy unit that performs between 4 and 6 elective cases daily. The obstetricians and nurses on this unit are very cooperative

and eager to engage in studies to improve patient care and outcome. In addition, there is a large anesthesia staff during the day that can assist in patient recruitment and data collection.

5) Study Design

This will be a prospective, randomized, double blind study. Patients presenting for primary elective cesarean section will be randomized into two groups. Consent for the study will be obtained in the pre-op area before the patient receives any medication. Group 1 will be the standard morphine group. In this group, the patient's will receive a spinal anesthetic consisting of 1.5cc of 0.75% bupivacaine plus 250mcg of preservative free morphine. Group 2 will be the experimental hydromorphone group. In this group, the patient's will receive a spinal anesthetic consisting of 1.5cc of 0.75% bupivacaine plus 50 mcg hydromorphone. This dose was chosen because it is equipotent to the standard dose of morphine used for cesarean deliveries, which is 250mcg. A second anesthesiologist will draw up the study medication and give the syringe to the investigator so that the investigator is unaware of what is contained in the syringe. The person drawing up the medication does not participate in patient evaluation.

Each patient will receive 500cc of Lactated Ringers within the 15 minutes prior to administration of spinal anesthetic. Each patient will also receive 4mg ondansetron immediately prior to spinal anesthetic.

After performing the spinal anesthetic, each patient will be positioned on the operating room table using standard left uterine displacement. Vitals will be recorded every minute for the first 10 minutes and then every 3 minutes for the remainder of the case. A decrease in BP > 30% of baseline along with a heart rate > 60 or if the patient has symptoms of hypotension (nausea, vomiting, dizziness, or lightheadedness) will be treated with phenylephrine 100 mcg IV boluses and repeated every 1 minute until BP returns to normal. If the HR is below 60, ephedrine will be used in 10mg increments as stated above. Additionally, a bolus of 100cc IV fluid will be given during each hypotensive episode. After the spinal is administered all patients will receive maintenance IVF at a rate of 150cc/hr.

The presence of nausea and vomiting, and pruritus will also be recorded in 5 minute intervals.

The dermatomal level of anesthesia will be assessed every 2 minutes until the anesthetic level reaches thoracic level 4 (t-4). We will test for adequate level of anesthesia with a needle testing for the sensation of a pin prick. .

Patient satisfaction will be recorded at the end of the procedure. Patients will be asked to rate their experience on a 1-5 scale as follows. 1-completely dissatisfied, 2-partially dissatisfied, 3-neutral, 4-partially satisfied, 5-completely satisfied.

All patients will have the same post op pain orders as is standard on the labor floor. These include ketorolac 30mg IV every 6 hours. In addition to this, every patient in this study will be given an IV fentanyl PCA (patient controlled analgesia) pump. The settings of the pump will be basal rate of 0, bolus rate of 15mcg, and a lock out of every 8 minutes. This allows a maximum hourly dose of 105mcg. The PCA pumps record how often the patient requested additional analgesia and how much total fentanyl the patient received per hour. The pumps will be queried at the end of 24 hours to record total fentanyl dose can record the total medication administered per hour over a 24 hour period.

The patients will then be followed hourly for the first 4 hours by the investigating team. Pain scores will be obtained using the verbal response scale (VRS). The VRS scale is measured using a score of 0 as no pain and 10 as the worst pain. The presence of nausea and pruritus will also be assessed at these time points. The patients will then be visited again at 6hrs, 12 hrs, and 24 hrs. At these time points, the patients will be asked for pain scores, presence of nausea, vomiting and pruritus.

At 24 hrs, the patients will be evaluated for overall satisfaction with pain control and their anesthetic experience.

a) Recruitment Methods

Every patient that presents for primary elective cesarean section will be a potential candidate for this study. After admission to the labor and delivery floor, the patient will be approached by a member of the investigating team. These patients will be informed about the trial and consent will be obtained. If the patient does not wish to take place in the trial, she will receive standard anesthetic care.

b) Inclusion and Exclusion Criteria

Inclusion Criteria for this study:
Elective primary cesarean section; Females age 18-40

Exclusion Criteria:
Emergency cesarean section; Anesthetic other than spinal; History of chronic pain or pre-op opioid use; Allergy to morphine or hydromorphone; BMI>40

c) Number of Subjects

Since there are no prior studies comparing Duramorph to hydromorphone for postoperative analgesia we cannot perform a power analysis to determine the number of patients required. We propose to enroll 20 patients, 10 per group, in a blinded fashion and collect our data as described above. We will then perform an interim analysis of the data to see how much fentanyl is being used in the hydromorphone and morphine group. At that point we will determine the total number of patients required and inform the IRB and update the protocol accordingly. We will not change the protocol in any way after analyzing the data.

d) Study Timelines

Each individual subject will be followed for 24 hours after cesarean section.
We anticipate that we will enroll all subjects within 1year.
We estimate that this study will be completed 6 months after enrollment of all subjects.

e) Study Endpoints

Each patient will receive a fentanyl pca (patient controlled analgesia) pump in the post anesthesia care unit (pacu). The primary outcome is total dose of fentanyl pca used in 24 hours. This will be a marker for supplemental analgesia needed after the cesarean delivery.
Secondary outcomes include:

1. Time to initial use of pca. We want to understand when the hydromorphone and morphine group will require the first supplemental analgesic.

2. Time frame of most frequent use of pca. When does each group use the pca most frequently? Between 1-4 hrs, 4-6 hrs, 6-12 hrs, 12-24 hrs? This will help us understand the duration of analgesic effect between hydromorphone and morphine.
3. Pain scores in both groups between the above time frames.
4. Patient satisfaction scores in the above time frames.
5. Assessment of nausea and vomiting and pruritus in the above time frames. This will help us understand the onset and incidence of these side effects among the two groups.

f) Procedures Involved in the Human Research

The study design was described above. Every patient will receive a spinal anesthetic, as is standard of care for primary elective cesarean section. All standard anesthetic safety protocols and all standard nursing protocols will be followed. The only difference is the use of the study drug.

Every patient in this study will be given a pca for post-operative analgesia. The nurses in the post anesthesia care unit and post-partum unit are familiar with pca use and are capable of assessing the patients for sedation and respiratory depression. All cesarean section patients already have to be monitored for respiratory depression in the first 24 hours. The nurses are therefore equipped and qualified to monitor the study patients. The study patients will get the same monitoring as every cesarean section patient in the post-partum unit.

Data will be collected as described above. Only data up to 24 hours will be obtained.

g) Specimen Banking

This is not applicable to the current study.

h) Data Management and Confidentiality

Data will be collected on paper that will indicate the patient's medical record and her study number assignment, and her initials. There will be no indication on these sheets of the patient's name. The data collection sheet is attached. The data on the sheets will be transferred to an Excel computerized spreadsheet without her initials. The excel data base is in a computer with a password. Also, the excel program is protected by a password. We will have a separate binder that will have the patients name along with her medical record # should we need to recheck records for any reason. The binder with the data sheet will be kept in the anesthesia research office (room KCC 840) that is kept locked at all times. The binder with the identifying information will be kept in the obstetric anesthesia office KP 2-58, also a locked office. Only the PI will have access to these records.

i) Provisions to Monitor the Data to Ensure the Safety of subjects

Dr. Jeffrey Silverstein will be responsible for the data safety and monitoring of this study. Dr. Silverstein is an independent anesthesiologist, who is not involved with this study. Dr. Silverstein has several years of experience serving on the Mount Sinai IRB. Using hydromorphone in the spinal anesthetic carries the same risks as using morphine, namely respiratory depression. As an anesthesiologist, Dr. Silverstein is qualified to assess the problems associated with this medication and with the complications of spinal anesthesia.

Indicate whether this person is the PI, a Team Member, or is Independent:
Independent Monitor
Last Name: Silverstein
First Name: Jeffrey
Academic Title: MD, Professor Anesthesiology
Department: Anesthesiology
Mailing Address: 1 Gustave L.Levy Pl
KCC 8th fl, NY NY 10029
Phone: 212-824-8200
Fax:
E-mail: jeff.silverstein@mssm.edu

Data will be reviewed at least monthly for completeness and accuracy by review of the database with review of the original datasheets if indicated. If our study was suspended on a temporary or permanent basis, the PI would report this to the IRB. In addition, any complications from the spinal anesthetic or the study drug would be reported to the Department of Anesthesiology PI committee and to the IRB.

j) Withdrawal of Subjects

Patients may be withdrawn from the study if adequate spinal block is not achieved, or if the patient develops post dural puncture headache.

6) Risks to Subjects

The risks to the patient undergoing spinal anesthesia for cesarean delivery are the same regardless of opioid used. The risks include post dural puncture headache, bleeding, bruising, infection at the site of insertion, and nerve damage, inadequate spinal or high spinal anesthetic. These are the risks of spinal anesthesia. The risks of morphine use include delayed respiratory depression, nausea, vomiting, and pruritus. These are the same risks of hydromorphone. There are no additional risks to the patient from the study intervention.

7) Provisions for Research Related Injury

As explained above, the risks to the patient are the same regardless of study drug. The risks come from the spinal procedure itself. Every patient is followed post operatively and assessed for complications and treated appropriately. The study patients will be treated the same in this regard

8) Potential Benefits to Subjects

The study drug, hydromorphone, may provide an improved analgesic profile to the patient. It may also decrease the side effects of nausea and pruritus.

9) Provisions to Protect the Privacy Interests of Subjects

Only patient initials will be used on the data collection sheet and this data will be stored on a password protected Mount Sinai computer. Only the PI will have access to the patient's identifiable information. Patients will be reassured that all their information will remain confidential.

10) Economic Impact on Subjects

There will be no additional cost to the patient for taking place in the study. The patient will be charged the standard anesthesia fee for cesarean section. There will be no additional fee for PCA use as this is part of the study and would not have been otherwise used in the care of the patient.

11) Payment to Subjects

There will be no payment to subjects for participation in the study.

12) Consent Process

Women will be enrolled in the study on the Labor and Delivery Unit of The Mount Sinai Hospital at the time of presentation for their primary elective cesarean section. Consent will be obtained in the pre-operative area. The surgical consent is also obtained at this time. If the patient is able to give consent for cesarean section in the pre-op area, then she can consent for this study as well.

The population of interest is pregnant women. Minors, cognitively impaired adults, and non-English speaking subjects will not be approached for inclusion in the study.

13) Process to Document Consent in Writing

The standard PPHS consent template will be used. The consent form is attached.

14) Vulnerable Populations

Indicate specifically whether you will include or exclude each of the following populations:

Include	*Exclude*	*Vulnerable Population Type*
	x	*Adults unable to consent*
	x	*Individuals who are not yet adults (e.g. infants, children, teenagers)*
	x	*Wards of the State (e.g. foster children)*
x		*Pregnant women*
	x	*Prisoners*

15) Multi-Site Human Research (Coordinating Center)

This is a single site study.

16) Community-Based Participatory Research

N/A

17) Sharing of Results with Subjects

Results will not be shared with the patients or their obstetricians.

18) IRB Review History

N/A

19) Control of Drugs, Biologics, or Devices

Note: The IDS has its own forms that must be completed and a review process that must be followed before the IDS representative will sign off on Appendix B for submission to the PPHS.

The Mount Sinai Labor and Delivery Unit utilizes a Pyxis machine, which stores and dispenses controlled substances. The pyxis is accessed by passcode and fingerprint. Currently the morphine used for cesarean section is stored in the pyxis and is accessed by identifying the patient and withdrawing the drug. The Pyxis records who took out the medication and the time of withdrawal. The hydromorphone will be stored in this secure pyxis machine as well.

References:

1. Mashour, G.A, Lydic R. Neuroscientific Foundations of Anesthesiology. New York: Oxford University Press, 2011.
2. Rauch, E. “Intrathecal Hydromorphone for Postoperative Analgesia After Cesarean Delivery: A Retrospective Study”. AANA Journal. 2012 Aug;80(4 Suppl):S25-32
3. Halpern, S.H et al. “Epidural Morphine vs. Hydromorphone in post-cesarean section patients”. Canadian Journal of Anesthesia. 1996; 43(6):595-598.

Statistical plan

Categorical variables were tested via chi-square test, while continuous variables were tested via t-test, paired t-test, Wilcoxon rank sum test, or Mann-Whitney U test where applicable.