DETAILED PROTOCOL **12/21/2020**

Principal Investigator

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Protocol Title

Intrathecal opioids for pain control after colorectal resection: determining the optimal dose

Background and Significance

Intrathecal (IT) opioids have been established as a safe and efficacious modality to treat postoperative pain.[1–9] In the setting of colorectal surgery, studies have shown that intrathecal opioids together with multimodal analgesic regimens provide pain relief superior to multimodal analgesia alone.[2] Furthermore, in the setting of multimodal analgesia, IT opioids also appear to be equianalgesic to epidural analgesia while conferring an improved safety profile.[10] As a result, many institutions have incorporated intrathecal opioids into their Enhanced Recovery after Surgery (ERAS) pathways.[1,2]

While morphine has traditionally been considered the "gold standard" in IT opioid therapy for postsurgical pain, hydromorphone has been gaining popularity as an alternative.[11] The doses ranging between 0.005 mg to 0.25 mg for hydromorphone[12–15] and 0.05 mg to 0.625 mg (with doses as high as 10 mcg/kg in the setting of cardiac surgery) for morphine[11,16] has been found to be efficacious in this patient population. However, increasing opioid doses are associated with increased incidence of adverse effects.[16,17] A meta-analysis reviewing twenty-eight studies which investigated intrathecal morphine versus placebo demonstrated moderate increases in the incidences of pruritus, nausea and vomiting.[13] In fact, the incidence of nausea with IT morphine has been reported to be 33%.[16] While hydromorphone is similar chemically to morphine, it is metabolized differently. Differences in pharmacokinetics may allow for differences in side effect profiles. Hydromorphone is more lipid soluble than morphine. 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. Some studies (performed in the women undergoing cesarean delivery) have also found that hydromorphone causes less nausea and pruritus than morphine[18], while others have not.[14,19,20]

Despite the widespread use of IT hydromorphone and morphine for pain after colorectal surgery, the optimal dose for neither drug has been established in prospective trials. We have previously performed a dose-finding study of IT hydromorphone and morphine in women undergoing cesarean delivery.[14] Briefly, 80 parturients scheduled for elective cesarean delivery were randomized to receive IT morphine or IT hydromorphone at a dose determined using up–down sequential allocation with a biased-coin design to determine ED_{90}, which was found to be 75 mcg for IT hydromorphone and 150 mcg for IT morphine. Our follow-up study also found no differences in adverse effects or efficacy between the drugs.[20] The results from the obstetric population, however, cannot be directly translated to the colorectal surgery population due to pharmacodynamic and pharmacokinetics differences related to the pregnancy, age, presence of comorbidities, differences in surgical techniques, and co-administration of IT local anesthetic.[3,21]

This study applies the methodology we have previously used in the obstetric population to the patients undergoing colorectal resection and aims to identify the optimal dose of IT hydromorphone and morphine that provides good pain relief without causing significant side effects. Secondarily, we will compare each drug at its optimal dose in terms of opioid consumption and side effects. Based on our prior findings, we hypothesize that the optimal dose of intrathecal

hydromorphone will be 75 mcg and the optimal dose of intrathecal morphine will be 150 mcg. Additionally, we hypothesize that exploratory findings comparing the two drugs at their optimal doses will show no difference in the incidence of adverse effects.

Specific Aims

Specific Aim 1: To determine the dose of IT hydromorphone that optimizes pain reduction after colorectal surgery.

Specific Aim 2: To determine the dose of IT morphine that optimizes pain reduction after elective colorectal surgery.

Specific Aim 3: To preliminarily compare the optimal dose of IT hydromorphone to the optimal dose of IT morphine for elective colorectal surgery in terms of pain reduction, side effects, and quality of recovery scoring.

Study Hypothesis

We hypothesize that the optimal dose of IT hydromorphone will be 75 micrograms, and the optimal dose of IT morphine will be 150 micrograms. Furthermore, we hypothesize that at respective optimal doses, IT hydromorphone will have a similar side effect protocol to IT morphine.

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 criteria:

1. Adult patients with an American Society of Anesthesiologists (ASA) physiological status I-III
2. Undergoing colorectal minimally invasive surgery (MIS)
3. Age between 18 and 75 years of age
4. Body mass index (BMI) between 18.5 and 40
5. Ability to understand and read English

Exclusion criteria:

1. Not able or unwilling to sign consent
2. Patients undergoing ileostomy closure
3. Patients undergoing ambulatory surgery or anticipated to be discharged sooner than 24 hours after surgery

4. Patients with chronic pain, requiring daily opioid use at the time of surgery
5. Patient intolerant or allergic to opioids, NSAIDs, or acetaminophen
6. Patients requiring emergent surgery
7. Any contraindication to neuraxial anesthesia (coagulopathy, localized infection at the site of injection, pre-existing spinal pathology, or peripheral neuropathy)
8. Any patients currently receiving any anticoagulation medication other than aspirin and who have not discontinued the medication per American Society of Regional Anesthesia anticoagulation guidelines[22], and/or an abnormal INR
9. Patients with hepatic or renal insufficiency in as much as the patient is not a candidate for acetaminophen or NSAIDs, respectively

All efforts will be made to enroll participants regardless of ethnic heritage, race, or gender. No passive recruitment methods (newspapers, advertisements, or flyers) will be used.

Subject Enrollment

Patients will be identified from the preoperative surgical listing schedule. Recruitment will ideally occur at the patient's last clinical visit prior to surgery. If not feasible, the patients meeting inclusion and exclusion criteria will be contacted by phone prior to scheduled surgery to review the study, have their questions answered while having the opportunity to think about the participation and discuss it with their family and friends. Only physician study personnel (HPS, AWA, JP, EES, JKP, DAO, AND, and JP) will approach potential subjects for recruitment. If patients express interest in participation, they will be approached again in the morning of the surgery, the consent form will be reviewed in detail with them, they will then have their final questions answered prior to signing the consent form.

A total of 80 subjects will be randomized to receive either IT morphine or hydromorphone as part of their spinal anesthesia. 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. Doses of IT hydromorphone and morphine will be selected according to a sequential up-and-down method, using a biased coin design to find the estimated dose at which 90% of patients would have desired pain control while minimizing side effects (ED_{90}). Given the sequential up-and-down design, the dose of the next patient will be based on "success" or "failure" of the prior patient. For that reason, if a patient withdraws from a study prematurely (i.e., before the primary outcome can be collected), the same dose will be repeated in the next patient. To account for the potential withdrawals/attrition, we plan to accrue a maximum of 85 patients. We anticipate that up to 120 patients will be screened to achieve the accrual goal.

Study Procedures

IT opioid preparation and dose selection

Following informed consent and randomization, an anesthesia provider not involved in patient care or assessment will prepare the opioid medication for IT injection. The dose of IT morphine or hydromorphone will be determined by an

up-and-down method utilizing a biased coin design. The initial starting dose of IT hydromorphone will be 50 micrograms. The initial starting dose of IT morphine will be 100 micrograms. The dose will be adjusted in subsequent patients as determined by its success (or failure) in providing good pain control, with success defined as numerical rating scale (NRS) 4 or less with movement at 12 hours and not requiring substantial doses of opioids (≤ 15 oral morphine equivalents (OME) within first 12 hours after IT opioid administration in the postoperative recovery time period). NRS with movement will be elicited by asking patients to cough and report their pain score, as described by Oh et al.[23] Doses for subsequent patients will be adjusted using a sequential up-and-down method utilizing a biased coin design as described by Durham et al.[24]

In the event that a patient is enrolled and the neuraxial space is not able to be accessed due to difficult anatomy, significant discomfort with placement, or patient refusal of placement, the patient will be withdrawn from the study and the subsequent patient enrolled will take their place and follow at the same analgesic dosing.

We are attempting to find the ED_{90} dose of IT opioid, which would correspond to 90% of patients obtaining "good" analgesia. When ED_{90} is to be determined (τ=0.9); the probability $B = (1-\tau)/\tau = (1-0.9)/0.9 = 0.1/0.9 \approx 0.11$. If no positive response is encountered, the dose is stepped up for the next patient. When a success is encountered, the next patient is randomized with probability $B \approx 0.11$ to the next lower dose and with probability $1- B = 0.89$ to the same dose.

Doses for intrathecal hydromorphone are as follows (in micrograms):
10 - 25 - 50 (starting dose) - 75 - 100 - 125 - 150 - 175 - 200

Doses for intrathecal morphine are as follows (in micrograms):
25 - 50 - 100 (starting dose) - 150 - 200 - 250 - 300 – 350 - 400

Definition of success:

1) NRS ≤4 at 12 hours after IT opioid administration

AND

2) Analgesic requirement ≤15 OME within 12 hours after IT opioid administration (excluding intravenous opioids given intraoperatively in the operating room or immediately postoperatively at the post-anesthesia care unit, PACU)

Definition of failure:

1) NRS score of > 4 at 12 hours after IT opioid administration

OR

2) Analgesic requirement of >15 OME within 12 hours after IT opioid administration (excluding intravenous opioids given either intraoperatively or in PACU)

The maximum dose of IT hydromorphone and morphine will be 200 micrograms and 400 micrograms, respectively. All patients will receive some amount of IT opioid (minimum 10 micrograms and 25 micrograms, respectively).

Preoperative care

Preoperatively, patients will be sedated, under the discretion of the anesthesiologist, with intravenous midazolam (1-2 mg) and fentanyl (50-100 mcg) for alleviation of anxiety and pain. Additional sedatives will be given at the discretion of the anesthesia team. The spinal injection will be performed in either seated or lateral supine position at the L3-4 or L4-5 interspace. Spinal anesthesia will consist of either morphine or hydromorphone according to study protocol and randomization. Normal saline will be used to dilute the total volume to 2 mL. 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 using hat, mask and sterile gloves during spinal placement.

Intraoperative care

Following the spinal placement, all patients will undergo general endotracheal anesthesia. All patients will receive a standard perioperative analgesic and antiemetic regimen (Figure 1). Additional intraoperative intravenous opioids will be given at the discretion of the attending anesthesiologist.

Postoperative care

Postoperatively, all patients will follow standardized multimodal analgesia pathway (Figure 1). Additional analgesic treatment will be given at the discretion of the care team. All patients will be monitored per institutional guidelines for administration of IT opioids which include remote pulse oximetry for 24 hours after administration.

Data Collection:

Each patient will be interviewed at 12 (±1) hours and 24 (±1) hours after IT opioid administration and the following data will prospectively gathered:

1) At 12 hours post IT opioid:
    a. NRS score for pain (0-10)
    b. Presence and severity of nausea (none, mild, moderate, severe)
    c. Presence and severity of pruritus (none, mild, moderate, severe)
    d. Overall benefits of analgesia score (OBAS)
2) At 18 hours post IT opioid:
    a. NRS score for pain (0-10)
    b. Presence and severity of nausea (none, mild, moderate, severe)
    c. Presence and severity of pruritus (none, mild, moderate, severe)
3) At 24 hours post IT opioid:
    a. NRS score for pain (0-10)

b. Presence and severity of nausea (none, mild, moderate, severe)
c. Presence and severity of pruritus (none, mild, moderate, severe)
d. Overall benefits of analgesia score (OBAS)
e. Quality of Recovery (QoR) 15 score
f. Overall satisfaction with IT opioids (satisfied, somewhat satisfied, neutral, somewhat unsatisfied, unsatisfied)
g. Has patient passed flatus (yes/no) or had bowel movement (yes/no)

QoR 15 is a multidimensional, valid, reliable, responsive, and easy-to-use method of measuring quality in patients' postoperative recovery, will be used as the secondary outcome measure.[25] Similarly, OBAS is a validated measure incorporating both effectiveness of pain control and unwanted effects related to analgesic treatment.[26]. Grading of nausea and pruritus (none, mild, moderate, severe) will be defined by the individual patient's perception of severity.

In addition, the following data will be collected from patient electronic medical records:

1) Total opioid consumption at 12 and 24 hours of IT opioid administration
2) Total non-opioid analgesic consumption within 12 and 24 hours of IT opioid administration
3) Medical treatment(s) for nausea or pruritus within 12 and 24 hours of IT opioid administration
4) Presence of respiratory depression within 12 and 24 hours IT opioid administration
5) Presence of sedation within 12 and 24 hours IT opioid administration
6) Length of hospital stay
7) Time of first flatus and bowel movement after surgery

The data that will be collected in this study are summarized in Table 1.

Study outcomes:

Primary Outcome: NRS score for pain at 12 hours after IT opioid administration

Secondary Outcomes:

1) NRS score for pain at 18 and 24 hours after IT opioid administration
2) Presence and severity of any opioid-related complication
   a) Pruritus
   b) Nausea
   d) Respiratory depression
   e) Sedation
   f) Postoperative ileus

3) Total opioid consumption (in OME)
4) QoR 15
5) OBAS
6) Overall subjective satisfaction with analgesia

Early end points:

1) Change patient's 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 perioperative analgesia and anesthetic care will be the responsibility of the patient and their insurance provider.

Statistical Analysis

NRS scores, nausea, and pruritus will be analyzed by ANOVA for repeated measures. Patient 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. For subjects who are withdrawn, the last observed values will be utilized. 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

As this is a dose-finding study, it is possible that medication doses of intrathecal hydromorphone and morphine that are less (or more) than what is commonly used in clinical practice may be used. However, any and every patient who experiences postsurgical pain will be treated with standard analgesic medications titrated to patient comfort, regardless of type and amount of intrathecal opioid used.

Approximately 10-40% of the time, nausea may occur. If nausea occurs, it will be treated and managed according to usual measures. Approximately 10-40% 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 <1% in non-obstetric population 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.

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 colorectal surgery.

Monitoring and Quality Assurance

Assurance of safety and tolerability:

Following continuous care during surgery, all patients will have a scheduled visit at 12 hours after intrathecal injection to evaluate the efficacy of analgesia. As noted, numerical rating scale (NRS) 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 patient condition will be dictated by the surgical, 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 surgical, 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. In addition, a safety committee, consisting of anesthesiologists not involved in the study, will be established prior to subject recruitment and will review any AE encountered in each patient, with emphasis placed on known AE related to acute opioid overdose, namely respiratory depression and sedation.

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.

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Study Activity	Pre-op	12±1 hours	24±2 hours	At discharge
Informed consent	x			
Inclusion/exclusion criteria	x			
Pain scores (NRS)	x	x	x	
Presence and severity of nausea	x	x	x	
Presence and severity of pruritus	x	x	x	
Flatus and bowel movement (yes/no)			x	
QoR-15			x	
OBAS		x	x	
Overall satisfaction with IT opioids			x	
Patient and surgical data collections by chart review	x			x

Table 1. Data collection overview. NRS, Numerical Rating Scale, QoR 15, Quality of Recovery 15; Overall Benefits of Analgesia Score, OBAS

Figure 1. Multimodal Analgesia Pathway for Colorectal Surgery

Preoperative Holding Area

- **Acetaminophen**
  - 1,000mg PO in preoperative area then followed by scheduled q6h dosing
- **Celecoxib**
  - 400mg PO (≤ 65 years old AND GFR >50 mL/min)
  - 200mg PO (>65 years old AND GFR >50 mL/min)
- **Scopolamine Transdermal Patch** (applied to skin behind the ear)
  - 1.5mg as needed for high-risk PONV (female, non-smoker, hx PONV/motion sickness)
  - Use sparingly for age >65 years (due to increased risk of adverse effects)
- **Caffeine**
  - Consider 200mg PO if patient consumes **caffeine** >100mg (1-2 cups of coffee or ≥3 caffeinated sodas) daily has not consumed **caffeine** prior to surgery

Intraoperative Care

- **General Anesthesia with Opioid Spinal** (dose of either morphine or hydromorphone per study protocol)
- **Antiemetic Therapy**
  - **Ondansetron** 4mg IV
  - **Dexamethasone** 0.1mg/kg up to 8mg IV
  - **Droperidol or Haloperidol** administration reserved for patients with history of severe PONV; female and non-smoker; or per anesthesiologist's discretion
  - **Propofol Infusion** for severe PONV risk, discuss with anesthesiologists
- **Ketamine** 10-40mg IV in divided doses
- **Ketorolac** 15mg IV at conclusion
- **Acetaminophen** 1000mg IV at conclusion of the case ***IF*** not given PO preoperatively
- **Opioid:** Prefer **fentanyl** (<300mcg); however choice is at discretion of the anesthesia team

Post-Anesthesia Care Unit (PACU)

- **Acetaminophen** 1000 mg PO or IV once for pain; review last dose before administering (>6 hours)

PRN Analgesics (use only one oral option at a time)

- **Oxycodone** 5-10mg PO every 4 hours prn; 5 mg for pain rated 4-6; 10mg for pain rated 7-10
- **Hydromorphone** *(For allergies or intolerance to oxycodone)* 2-4mg PO every 4 hours prn; 2mg for pain rated 4-6; 4mg for pain rated 7-10

Breakthrough IV Pain Medications

- **Ketamine** 10mg IV every 10 min prn for pain scores 4-10 (Goal of around 10-40mg IV throughout perioperative period)
- **Ketorolac** 15 mg IV (additional dose) at the discretion of anesthesiologist
- **Fentanyl** 25mcg IV every 2 min prn for pain scores 4-10 for up to a total of 200 mcg
- **Hydromorphone** *(For fentanyl allergy/intolerance)* 0.2mg IV every 5 min prn for pain scores 4-10 for up to a total of 2mg
- **Antiemetics** (Administer 1st Ondansetron → 2nd Granisetron → 3rd Droperidol/Haloperidol)
  - **1st: Ondansetron** 4mg IV every 6 hours (check to see if given in OR)
  - **2nd: Granisetron** 1mg IV once
  - **3rd: Droperidol/Haloperidol:** 0.625mg IV every 6 hours (total of 2 doses, RASS must be -2 or higher to administer