Proposed Research Protocol Form
Northwestern University Medical School
Department of Anesthesiology Research Committee

Title: The Postoperative Analgesic Efficacy of Varied Concentrations of Ropivacaine Used for the Transversus Abdominis Plane (TAP) Block After Cesarean Delivery

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1.0 Research Aims:

.1 Research Questions(s): Is there a difference in postoperative analgesic efficacy between placebo, 0.2% ropivacaine, 0.5% ropivacaine, or 0.75% ropivacaine for a transversus abdominis plane (TAP) block for morbidly obese parturients as part of a post-cesarean delivery multimodal analgesic regimen that does not include intrathecal morphine?

.2 Hypotheses: Utilizing 0.5% ropivacaine in a TAP block, as part of a post-cesarean delivery multimodal analgesic regimen that does not include intrathecal morphine, will result in decreased 24 hour postoperative hydromorphone consumption compared to 0.2% ropivacaine and placebo, and will be equivalent in 24 hour postoperative hydromorphone consumption compared to 0.75% ropivacaine.

2.0 Research significance:

.1 Background: Cesarean delivery is the most commonly performed surgical procedures in the United States today, with over 1.2 million cases performed in 2005.[1] One of the most important aspects of cesarean delivery is the provision of safe, effective postoperative analgesia for the mother, while simultaneously ensuring minimal side effects for both the mother and neonate. Studies have suggested that a multimodal approach to post-cesarean pain utilizing both intravenous, oral, and neuraxial opioids and non-steroidal anti-

inflammatory drugs is highly effective in providing effective analgesia.[2-4]

A significant component of post-cesarean pain is incisional pain from the Pfannenstiel incision on the anterior abdominal wall.[5] The sensory supply to the skin, muscles, and parietal peritoneum of the anterior abdominal wall is derived from the anterior rami of T7-L1. After exiting the spinal column, these nerves proceed through the lateral abdominal wall within the transversus abdominal fascial plane, terminating in the anterior abdominal wall.[6,7]

Recent studies have suggested that blocking these afferent sensory nerves with local anesthetics, as part of a multimodal postoperative pain regimen, provides superior pain relief in terms of decreased pain scores and morphine consumption for up to 48 hours postoperatively.[8-10] The technique utilized for these studies employed a surface anatomical approach to the transversus abdominal fascial plane via the lumbar triangle of Petit, a technique validated in both cadaveric and radiologic studies.[11] However, as ultrasonography has emerged as the "gold standard" for initiating many nerve blocks, reports have described the successful use of ultrasound imaging for initiation of transversus abdominis plane (TAP) blocks for both abdominal surgeries and cesarean deliveries.[12,13]

In the published studies investigating the use of the TAP block for post-operative analgesia, either ropivacaine or bupivacaine was utilized in concentrations of 0.75% and 0.375%, respectively.[8,10] Studies comparing ropivacaine with bupivacaine for use in interscalene, femoral, or sciatic nerve blocks have found no difference in terms of potency, time to onset or duration of postoperative analgesia between the two local anesthetics.[14-16] Although no similar studies have been done with TAP blocks, one can assume that utilization of ropivacaine for this nerve block would yield similar results in terms postoperative analgesia. Moreover, the cardiotoxicity of ropivacaine has been shown to be significantly less than bupivacaine, making it a safer alternative for use in nerve blocks when used in high doses.[17,18]

Risk factors for respiratory depression after the administration of neuraxial opioids in the non-obstetric population include morbid obesity and obstructive

sleep apnea. For the obstetric population, a study of 856 patients revealed that all 8 patients who experienced respiratory depression after intrathecal morphine for cesarean delivery were markedly obese.[19] Furthermore, the onset of respiratory depression after intrathecal morphine can occur up to 12 hours after administration, a time period when the patient is not being as closely monitored as she is during the 1:1 nursing care in the recovery room. Therefore, it is our policy on the Labor and Delivery unit to not administer intrathecal morphine to any parturient with a history of obstructive sleep apnea or a BMI > 40 kg/m^2. As such, these patients often require intravenous opioid patient-controlled analgesia postoperatively, which has been shown to provide inferior pain relief and greater opioid consumption than neuraxial opioids.[20] Moreover, the current clinical standard is to administer the TAP block to those patients who have not received morphine in their neuraxial anesthetic.[8] Hence, the TAP block offers a novel addition to the management of post-cesarean pain for this patient population.

Since there have been no published dose-response studies investigating the effective analgesic dose of ropivacaine for use in a TAP block for post-Cesarean delivery analgesia, we propose a study primarily examining the effect on 24 hour post-Cesarean delivery opioid consumption of using either a placebo, 0.2% ropivacaine, 0.5% ropivacaine, or 0.75% ropivacaine for TAP blocks.

.2 <u>Literature</u>:

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.3 Significance:

Breakthrough pain in the postoperative period is a common occurrence. Currently, we attempt to effectively control this breakthrough pain with a combination of intravenous and oral non-steroidal anti-inflammatory drugs and opioids. However, this drug regimen has its limitations, especially opioids. Opioid therapy is laden with side-effects including nausea, vomiting, constipation, sedation and pruritus. Opioids also cross into breast milk and have been detected up to 72-hours after cesarean delivery, although their clinical effect on the neonate has not been determined.[21] TAP blocks have been shown to decrease overall morphine consumption after cesarean delivery, as well as decrease the amount of postoperative pain reported by patients.[8] The advantages of improved pain control include: improved patient satisfaction, prevention of postoperative complications associated with pain (e.g., atelectasis), improved ability of the mother to care for her newborn, and decreased side-effects from systemic opioid analgesia. In addition, the

reduction in need for postoperative breakthrough pain medications following cesarean delivery may minimize the consumption of resources (e.g., RN administered rescue medications) required to manage breakthrough pain on the postpartum wards. Furthermore, in morbidly obese patients, the potential reduction in postoperative opioid consumption afforded by a TAP block would also decrease the risk of respiratory depression, for which these patients are at a higher risk. Finally, improved postoperative pain control results in earlier ambulation, thereby reducing the risk of developing deep venous thrombosis and possible thromboembolic events, which is the number one cause of maternal mortality in the United States.[22,23]

An additional benefit of the TAP block in post-cesarean analgesia is its potential to reduce the incidence of post-operative neuropathic pain. A recent cohort study revealed that one-third of patients who underwent a cesarean delivery via Pfannenstiel incision had chronic pain at the incision site two years later, with 7% of patients rating their pain as moderate-to-severe.[5] Of those patients who rated their pain moderate-to-severe, neuropathic pain secondary to nerve entrapment was found to be the cause in 53% of the cases, based on history and physical exam findings.[5] Furthermore, one study has demonstrated that the intensity of acute post-operative pain is a significant predictor of the development of chronic neuropathic pain.[24] Therefore, based on this data, it would seem that the improved post-operative analgesia regimen provided by the TAP block may potentially reduce the incidence of post-operative neuropathic pain in this patient population.

The outcomes of this study will therefore allow us to establish an effective analgesic dose of ropivacaine, based on differences in concentration, for use in TAP blocks as part of a post-Cesarean delivery multimodal analgesic regimen that does not include intrathecal morphine.

3.0 Investigational Plan

.1 **<u>Study design:</u>** Randomized, double blind placebo controlled trial.

.2 Methods:

.2.1 Size of study groups(s):

The primary outcomes for this study will be 24-hour post-TAP block hydromorphone consumption. Secondary outcomes will be time to first request for hydromorphone, diameter of cutaneous sensory block from TAP block at 6 hours after placement, postoperative pain scores, 48-hour hydrocodone consumption in milligrams, 72-hour cumulative opioid consumption in morphine-equivalents, 24 hour ketorolac consumption in milligrams, 48 hour ibuprofen consumption in milligrams, incidence and severity of postoperative neuropathic pain at 1 and 6 weeks after completion of surgery, and incidence of side effects from opioids (nausea, pruritis, sedation).

There will be four groups used in this study:

a. Group 1 (Placebo Group) – 15mL 0.9% normal saline per side
b. Group 2 – 15mL 0.2% 60mg ropivacaine per side
c. Group 3 – 15mL 0.5% 150mg ropivacaine per side
d. Group 4 – 15mL 0.75% 225mg ropivacaine per side

For the purpose of sample size calculation, we assumed that a clinically important reduction in 24 hour hydromorphone consumption would be a 25%, 37.5% and 50% absolute reduction, compared with control, with increasing ropivacaine concentrations. The projected amount of 24 hour hydromorphone consumption in each group is assumed to be 4, 3, 2.5, and 2 mg. The projected amount of 24-hour hydromorphone consumption in for the placebo group is based on data obtained from a study by Palmer, et al. investigating the dose-response relationship of intrathecal morphine for postcesarean analgesia.[25] Using these assumptions a

one-way design with 4 groups with sample sizes of 46, 46, 46, and 46 was derived. The null hypothesis is that the standard deviation of the group means is 0.0 and the alternative standard deviation of the group means is 0.7. The total sample of 184 subjects achieves a power of 0.810 using the Kruskal-Wallis Test with a target significance level of 0.05 and an actual significance level of 0.046. The average within group standard deviation assuming the alternative distribution is 3.0. These results are based on a 2000 Monte Carlo sampling from the null distributions. However, in order to account for potential drop-outs, 50 patients will be recruited for each group, for an n=200 patients.

.2.2 Patient entry, exclusion and dropout criteria:

Inclusion Criteria: ASA II-III patient ≥ 18 years of age who is pregnant, presenting for a cesarean delivery via Pfannenstiel incision who is eligible to receive a spinal anesthetic with 0.75% bupivacaine and fentanyl and whose is not eligible to receive intrathecal morphine due to a BMI ≥40 kg/m^2.

Exclusion criteria: < 18 years of age; contraindication to placement of a spinal anesthetic; contraindication to use of non-steroidal anti-inflammatory drugs (NSAIDs); patients receiving medical therapies considered to result in tolerance to opioids; patients with a history of established chronic pain, (e.g. chronic low back pain, fibromyalgia or headaches), defined as requiring regular medical follow-up with pain specialists, as well as recent use (within the year preceding pregnancy) of opioid analgesics as an outpatient; patients with a history of diabetes mellitus; patients undergoing a vertical midline skin incision; patients who are undergoing a cesarean delivery after a failed vaginal trial of labor with neuraxial analgesia already in place;

Dropout criteria: intraoperative conversion to general anesthesia, failure of spinal anesthetic to achieve an adequate surgical level (loss of T4 dermatome to pinch bilaterally), failed spinal anesthetic requiring repetition of neuraxial blockade, and patients requiring >100 μg of intraoperative fentanyl for supplemental analgesia.

.2.3 Protocol specific methods:

Eligible women for elective cesarean delivery admitted to the Labor and Delivery Unit of Prentice Women's Hospital will be approached for study participation immediately after the routine preanesthetic evaluation or immediately after completion of the surgical procedure. Women who agree to participate will give written, informed consent at this time.

Subjects will be prepared preoperatively in the usual fashion with intravenous (IV) access, aspiration prophylaxis and intraoperative monitoring. Preincision antibiotics will be given and uterotonic medications will be used as per usual practice after delivery.

The anesthesiologist will perform a spinal anesthetic per routine with the subject in the sitting position using sterile technique at the L3-4 interspace (± one vertebral interspace) utilizing a 25-gauge Pencan spinal needle. The spinal anesthetic will consist of 12 mg of hyperbaric 0.75% bupivacaine + 15 μg fentanyl. The subject will be placed supine with left lateral tilt to alleviate aortocaval compression. Cesarean delivery will commence after adequate anesthesia is assured to a T4 sensory level to pinprick. Vasopressors and IV fluids will be administered at the anesthesiologist's discretion per usual practice.

Upon completion of the cesarean delivery, the subject will be transported to the post-anesthesia care unit (PACU). At the time of presentation to PACU, the subject will be randomized to one of four groups using a computer generated random number table: placebo (0.9% normal saline), 0.2% ropivacaine, 0.5% ropivacaine, or 0.75% ropivacaine. Randomization assignments will be kept in sequentially numbered opaque envelopes. The envelope will be opened by a research nurse who will prepare 2 x 20 mL syringes, each containing 15 mL of the assigned solution, with each syringe labeled "study drug". Subjects randomized to one of the ropivacaine groups will receive a total of 30 mL (15 mL per side) of ropivacaine according to group assignment. Subjects randomized to the placebo group will receive a total of 30 mL preservative free saline (15 mL per side).

TAP blocks will be performed within 15 minutes of arrival into the PACU room. All TAP blocks will be performed by one of five co-investigators (CC, AD, NH, AL, or EY), each of whom has significant experience in placement of these blocks. During block placement, the patient will be continuously monitored with non-invasive blood pressure measurement, EKG, and pulse oximetry. All patients will be placed in the supine position, with arms elevated above their heads. Utilizing a Sonosite M-Turbo Ultrasound machine with an L-25 transducer (5.0-10.0 MHz) (SonoSite, Inc., Bothell, WA), the abdominal muscle layers will be located by placing the ultrasound transducer perpendicular to the coronal anatomic plane at the T-10 dermatome level in the patient's midaxillary line. Three muscle layers (from superficial to deep: external oblique, internal oblique, and transversus abdominis) and three fascial layers (from superficial to deep: layer between subcutaneous fat and external oblique, layer between

external oblique and internal oblique, and layer between internal oblique and transversus abdominis) will be identified. Under ultrasound guidance utilizing an in-plane approach, a 70mm or 90mm, 21 gauge blunted Stimuplex needle will be advanced from the skin until the tip reaches the fascial layer between the internal oblique and transversus abdominis. After negative aspiration, 15 mL of the study drug will be injected incrementally, while simultaneously observing for distention of this fascial plane with local anesthetic. The needle will then be removed and the process repeated in the same manner on the patient's opposite side. Following completion of the TAP block, the patients will be monitored in the PACU per routine Labor and Delivery Unit guidelines.

As part of their postoperative pain control management, all patients will receive ketorolac tromethamine 30mg IV q6h x 24 hours, beginning within 30 minutes after completion of the TAP block. After 24 hours, ibuprofen 600mg per os will be administered q6 hours prn pain x48 hours. The patient will also receive patient-controlled intravenous hydromorphone analgesia (PCA), which will be set up within 30 minutes upon arrival to the PACU. The PCA will be set at 0.3mg bolus, lockout interval 10 minutes, with a 4 hour maximum dose of 5 mg. The PCA will be activated at patient's first request for supplemental analgesia and a VAS pain score will be documented at this time.

Prior to transfer to the floor, the labor and delivery nurse will notify the accepting floor nurse, through the nursing handoff report, of the patient's participation in this study. Also, a sheet will be placed on the front of the patient's chart, identifying the patient's participation in this study and instructing the floor nursing

staff to contact the anesthesia nurse clinician (and not the obstetric housestaff, as per routine) for evaluation and management of breakthrough pain. If the anesthesia nurse clinician deems that a change in the patient's pain management regimen is necessary, she will consult an anesthesiology physician on call, who will adjust the pain medications accordingly.

The patient will remain on the PCA for 24 hours after the time of TAP block placement, after which time the patient will be converted to acetaminophen/hydrocodone 325mg/10mg per os q4 hours prn pain x48 hours. These are routine oral analgesic medications for postoperative cesarean delivery analgesia in patients who do not receive intrathecal morphine.

Standard orders will be written for monitoring sedation and respiratory rate, and treatment of side effects (nausea, vomiting, pruritus and respiratory depression). The total amount of hydromorphone and hydrocodone given will be determined for each subject after 24 and 72 hours, and will be reported in milligrams; the total opioid consumption of 72 hours will be reported in morphine-equivalents. The total amount of ketorolac given will be determined for each subject at 24 hours; the total amount of ibuprofen given will be determined for each subject at 72 hours.

Time to first request for hydromorphone PCA; presence and severity of pain, nausea, and pruritus; extent of cutaneous sensory block; and 1 and 6 week postoperative follow-up will be made by an anesthesia nurse clinician blinded to group allocation, as follows:

Pain, nausea, sedation, and pruritus will be assessed at 2, 6, 24, and 72 hours after TAP blockade. Pain severity will be assessed both at rest and with movement (hip flexion) utilizing a verbal pain scale (0 = no pain, 10 = worst pain imaginable). Pain severity will also be assessed at the time of first request for PCA analgesia.

Nausea will be measured using a categorical scoring system (0 = none, 1 = mild, 2 = moderate, 3 = severe). Rescue antiemetics will be offered to any patient complaining of nausea or vomiting, per standard postoperative order regimen. Pruritus will be measured using a categorical scoring system (0 = none, 1 = mild, 2 = moderate, 3 = severe). Sedation will be measured using the Observer's Assessment of Alertness/Sedation Scale, a validated scale of sedation (see figure below).[26]

Observer's Assessment of Alertness/Sedation Scale (OAA/S)[24]

Response	Speech	Facial expression	Eyes	Composite score
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words			2
Does not respond to mild prodding or shaking				1
Does not respond to noxious stimulus				0

Assessment of cutaneous sensory block will be made at 6 hours post-TAP blockade, utilizing a similar method described in a study by Lavand'homme, et al. [27] Using an alcohol-sterilized von Frey hair (396 m Newton) the patient's abdomen will be stimulated, starting at the umbilicus and moving cephalad by 1-cm steps until the patient reports a distinct change in perception. Then, the

abdomen will be stimulated in the same fashion, again beginning at the umbilicus and moving laterally in one direction in 1-cm increments until the patient reports a distinct change in perception, and then laterally from the umbilicus in the opposite direction in 1-cm increments. Finally, the inguinal creases will be stimulated in the same fashion, beginning immediately beneath the bandage and moving in 1-cm increments caudad until the patient reports a distinct change in perception. These measurements will then be transcribed onto graph paper and the total surface area will be calculated.

The following data will be collected in addition to the primary and secondary outcome data: maternal age, height, weight, gestational age, history of previous abdominal surgery, and history of previous cesarean delivery.

Protocol specific analgesic regimens will end at 72 hours post-TAP blockade. 72 hours is chosen as the time to end the standardized analgesic regimens as this is the average time when post-cesarean delivery patients are typically discharged from the hospital.

Two telephone follow-up evaluations will be made (one at 1 week post-delivery and one at 6 weeks post-delivery) to assess the incidence and extent of postoperative neuropathic pain. These two follow-up evaluations will each use a combination of 2 pain questionnaires: the Neuropathic Pain Questionnaire—Short Form (NPQ-SF) and the Neuropathic Pain Symptom Inventory (NPSI) (see attached form). The NPQ-SF will be used to assess for the presence of neuropathic pain, while the NPSI will be used to assess for the type and severity of neuropathic pain. The NPQ-SF has been shown to have 64.5% sensitivity, 78.6% specificity, and 73%

accuracy for the presence of neuropathic pain[28]; the test-retest reliability and validity of the NPSI has also been demonstrated in the literature.[29]

.2.4 **Risks/Benefits:** The risks of the spinal procedure itself are unchanged by participating in this study. These risks include: ineffective anesthesia, pruritus, nausea, vomiting, and hypotension. Less common risks include fetal bradycardia or maternal postdural puncture headache. Rare complications include maternal or fetal respiratory depression, total spinal anesthesia, a toxic reaction to the anesthetic agents, and bleeding or infection in the epidural or spinal space that may lead to nerve damage. There is always a risk of inadequate analgesia after surgery with the proposed pain management regimen. Participation in this study does not increase this risk above baseline.

The risks of ropivacaine:

hypotension (37.0%)

nausea (24.8%)

vomiting (11.6%)

bradycardia (9.3%)

fever (9.2%)

pain (8.0%)

postoperative complications (7.1%)

anemia (6.1%)

paresthesia (5.6%)

headache (5.1%)

pruritus (5.1%)

back pain (5.0%)

Additional potential risks are present with the administration of a TAP block. These risks include: ineffective analgesia, soreness

around injection site, and mild bruising around injection site. Rare complications include inadvertent peritoneal puncture, systemic toxicity from local anesthetic, and bleeding or infection. The risk of inadvertent peritoneal puncture is potentially reduced by usage of ultrasound to confirm needle position.

Finally, risks due to participation in this study include loss of confidentiality. There is also a risk the patient may become emotionally uncomfortable since research nurses will be contacting patients at home for follow-up.

2.2.5 Confidentiality:

Subjects' identity will be guarded by assigning a numerical code which is only known by the principal investigator. Data is stored in department computer which is password protected. Each study subject will be assigned a study code number. The code will be used to link study data to patient identification (name) in a separate database. Subject data will be stored on secure computers at Northwestern University. Data access will be password protected and only available to study investigators. The surveys will have the study code affixed after they have been received from the mail.

4.0 Data Analysis:

.1 Data collection form: See attached.

.2 Data evaluation: The primary outcome (24-hour hydromorphone consumption) will be compared among groups using the Kruskal-Wallis test. Post hoc testing will be performed using the Mann-Whitney test with Bonferroni correction. The time to first request for analgesia will be compared using the log-rank test. The area of abdominal analgesia, 48-hour hydrocodone consumption, 72-hour cumulative opioid consumption, 24 hour

ketorolac consumption, 48 hour ibuprofen consumption, VAS pain scores and NRS scores for nausea, pruritus and sedation, and follow-up questionnaires will be compared using ANOVA or the Kruskal-Wallis H test. The incidence of side effects will be compared using a χ^2 statistic. A $P<0.05$ will be required to reject the null hypothesis.

.3 Interpretation of Anticipated Results: It is anticipated that a concentration of ropivacaine will be found that will provide effective post-cesarean delivery analgesia as part of a multimodal analgesic regimen that does not include intrathecal morphine. In turn, anesthesiologists will be able to provide superior post-cesarean analgesia with the TAP block for those patients who are ineligible to receive intrathecal morphine. Furthermore, it is anticipated that use of the TAP block will decrease the incidence of post-operative neuropathic pain after cesarean delivery.

5.0 Budget:

.1 Materials: all materials and medications utilized for this study are readily available on the Labor and Delivery Unit or from the Prentice Women's Hospital Pharmacy.

.2 Labor Requirements: existing anesthesia personnel on Labor and Delivery Unit.

.3 Presentation Cost: anticipated presentations at SOAP and ASA meetings.

6.0 Consent: See Attached