Official title:	Prospective Effect of Intravenous Ketorolac on Opioid Use, EBL and Complications Following Cesarean Delivery
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Basic study design:

Randomized Control Trial: Double-Blind Placebo-Controlled Trial

Study population and assembly of patients:

We will study 70 healthy (ASA 1 or 2) women between 18 and 45 years old with singleton term pregnancies undergoing or non-scheduled, non-urgent primary or repeat Cesarean delivery between 37-42 weeks gestational age with neuraxial anesthesia with combined spinal-epidural placed for surgery.

Exclusion criteria are as follows: unable or unwilling to provide informed consent, urgent or emergent Cesarean delivery, multiple fetal gestations (>1 intrauterine pregnancy), patients undergoing Cesarean delivery for bleeding such as placental abruption or actively bleeding placenta previa or vasa previa, contraindication to NSAID use eg: allergy, chronic renal disease, acute or chronic platelet dysfunction (e.g.: idiopathic thrombocytopenic purpura, HELLP syndrome), platelets <100k, history of peptic ulcer disease, inherited or acquired coagulopathies or bleeding disorder, (disseminated intravascular coagulopathy, hemophilia), suspected or proven placenta accreta, increta or percreta, inability to receive epidural morphine, patients with a diagnosed chronic pain disorder on chronic adjunct or opioid analgesia, use of general anesthesia during procedure.

Intraoperative exclusion criteria include an EBL > 1000 ml prior to cord clamp.

Randomization & Blinding:

Patients will be randomized to receive either ketorolac 30 mg in 1 ml (n=35) or normal saline 1 ml (n=35). Randomization will be performed by the Investigational Pharmacy in a block of four design. No one involved with patient care, enrollment or data collection will have access to the unblinding key until completion of the study. The randomization key will be kept in the Investigational Research Pharmacy, and they will prepare the medications accordingly. Upon arrival in the OR, the anesthesiologist will open an envelope that will contain the kit number corresponding to the patient's study identification number. The anesthesiologist or anesthetist will remove the assigned kit from the Omnicell. Patients, clinicians and study staff will be unaware of the patient's assigned study group. Upon study completion by all patients, the randomization key will be provided to the study staff upon request.

Brief Study Methods:

After obtaining written informed consent, the Investigation Research Pharmacy an envelope that will contain the kit number corresponding to the patient's study identification number. Basic demographic information is collected from the patient. Each patient will undergo combined spinal-epidural anesthesia with our standard cesarean induction dose of hyperbaric 0.75% bupivacaine 1.5 ml intrathecally and fentanyl 100mcg epidurally. The patient will be moved to the supine position with left lateral uterine displacement. When a T6 sensory level to pinprick is achieved, Cesarean delivery will proceed using the standard procedures established in our institution. Once the newborn is delivered and the cord is clamped, the first dose of the ketorolac/placebo will be administered by the anesthesiologist or anesthetist. Any additional medications required for sedation or pain control during the remainder of the surgery (hydromorphone and acetaminophen) will be given, as appropriate for patient comfort. Prior to the completion of the procedure, the patient will receive epidural morphine 3 mg per the standard protocols. Postoperatively, the patient will receive the corresponding three additional

scheduled doses of ketorolac/placebo every 6 hours. Supplemental analgesia will be administered according to a standard post-operative pain management protocol on labor and delivery with acetaminophen and intravenous hydromorphone provided, as needed for pain control.

Exposures and their measurement:

Exposure: Ketorolac 30 mg IV or Normal Saline 1 ml (Placebo) IV

Measurements: See outcomes and their measurements

Outcomes and their measurement:
Primary outcome: Estimated Blood Loss (EBL) will be compared between groups.

Secondary outcomes: Rate of Post-Partum Hemorrhage, Corrected Change in Hct on POD1, Uterotonic Doses, Units of Packed Reb Blood Cell Transfused, Hydromorphone Use, Total Hydromorphone Dose, Anti-emetic Doses, Pruritus Doses, Percentile Change in Systolic Blood Pressure at 6, 12, and 24 hours, Percentile Change in Diastolic Blood Pressure at 6, 12, and 24 hours, and Pain score at 0 and 15 minutes and 1, 6, 12 and 24 Hours post-Cesarean Delivery.

Confounders and their measurement:

Many confounders should be limited by the nature of an RCT in a select patient population and pre- and intra-operative exclusion criteria. Additional potential confounders, including intraoperative fluid volume administration and patient adherence to study medication, will be recorded. Posthoc analysis will be performed to determine if any differences between groups were significant.

Analysis plan:

Data will be assessed for normality using histograms, QQ plots and Shapiro-Wilk test. Demographic, obstetric, and perioperative data will be presented as mean (standard deviation), median [interquartile range] or count (percentage), as appropriate. Between-group comparisons will be assessed using the t-test and Wilcoxon signed-rank test, as appropriate. For dichotomized outcomes, a Chi-square test will be performed to assess the proportions between groups.

Sample size justification:

A priori power analysis was performed to determine the sample size. Based on our prior retrospective study, we knew that the mean estimated blood loss for uncomplicated Cesarean deliveries was 814 ml with a standard deviation of 242 ml. We set our difference between groups to 186 ml. This would detect an EBL of >1,000 ml in the ketorolac group, a value large enough to classify the ketorolac group as post-partum hemorrhage and potentially escalate care and lead to additional maternal morbidity. With an alpha error of 0.05 and a power of 80%, we estimated that a sample size of 28 patients per group would be needed or 56 total patients enrolled. We had concern for loss after enrollment due to acuity, cases after 4 pm and exclusion criteria including intraoperative EBL and obstetric refusal. We planned for the loss of 20% of enrolled patients and increased the total study enrollment number to 70.