Dosing of Ketorolac Impacts post-cesarean paiN manaGemenet (KING): A Randomized Controlled Trial

Protocol Proposal

Joe Eid, MD
The Ohio State University

Kara Rood, MD
The Ohio State University

Madeleine Caplan, MD
The Ohio State University

Maged Costantine, MD
The Ohio State University

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1.0 Introduction

1.1 Study Abstract

Postoperative pain management is always an evolving field especially in pregnancy where dosage of certain medications might be affected by the physiologic changes associated with pregnancy. Efforts have been made to create postoperative pain protocols to decrease opioids use. Ketorolac, a non-steroidal anti-inflammatory drug (NSAID), is one of the most commonly used medications after cesarean section. Limited guidance exists on the most effective dosing of ketorolac administered immediately postoperatively after cesarean section. Furthermore, there is limited data on the pharmacokinetics of ketorolac during the postpartum period and whether higher dosing would improve pain management.

1.2 Primary Aim

To compare the morphine milligram equivalents (MME) use in the first 24 hours postoperatively after cesarean section in patients receiving a single dose of 30 mg intravenous ketorolac vs. 60 mg intravenous ketorolac in the operating room after the end of surgery.

1.3 Primary Hypothesis

Among pregnant individuals delivering by cesarean section, a single dose of 60 mg intravenous ketorolac immediately postoperatively decreases the MME use in the first 24 hours following surgery compared to a single dose of 30 mg intravenous ketorolac.

1.4 Secondary Aims

The secondary aims of this study are to assess the MME use during the hospital stay, patient reported pain scores in first 24 hrs post-op, and time to first administration of opioid pain medication post-cesarean.

2.0 Background

In 2020 31.7% of all pregnancies in the United States were delivered via cesarean section.[1] For mothers undergoing cesarean delivery, optimal postoperative pain control is important, and there is a continued movement to decrease opioid consumption due to the addictive nature and adverse effects of these medications.[2] Many centers have implemented multimodal postoperative pain control protocols with the goal of improving analgesia and decreasing postoperative opioid requirements following cesarean delivery.[3,4] Ketorolac, a potent non-steroidal anti-inflammatory that can be administered via intravenous, intramuscular or oral route, is commonly used as a part of these protocols. The use of perioperative intravenous ketorolac has been shown to be beneficial in postoperative analgesia in non-obstetric patients. Further, there is data to show that the use of ketorolac in multimodal analgesia protocols can reduce post-operative opioid requirements in the first 24 hours following cesarean delivery without increasing postoperative complications.[5,6]

The optimal dose of ketorolac following cesarean delivery is not yet clear. The standard manufacturer recommended dose for ketorolac is 30 mg IV for adults less than 65 years of age without renal dysfunction. One retrospective study in obstetric patients found no difference in opioid requirements at 24 hours in patients who received a 15 mg vs 30 mg parental dose at the time of cesarean.[7] A meta-analysis in non-obstetric patients demonstrated a reduction in postoperative opioid use following a perioperative loading dose of ketorolac 60 mg IV, but no difference between a 30 mg IV dose and placebo.[8] A third study in emergency department

patients saw no difference in pain scores at 30 minutes among patients who received ketorolac 10 mg, 15 mg, and 30 mg IV doses and hypothesized that there may be a “ceiling” effect.[9]

Additionally, there is limited data regarding the pharmacokinetics of ketorolac in the immediate postpartum period. Ketorolac is a non-selective cyclooxygenase inhibitor, which works to inhibit prostaglandin synthesis providing anti-inflammatory and analgesic effects.[10] The altered physiology of pregnancy, including increased glomerular filtration, distribution volume, and delayed gastric emptying have been known to alter the pharmacokinetics of many medications. Thus, it is plausible that the pharmacokinetics of ketorolac will be altered in the peripartum state.[6] There is data to suggest that ketorolac has both increased clearance and increased distribution volume in patients at the time of cesarean delivery, compared to their non-pregnant peers.[11,12] This suggests that a larger loading dose of ketorolac may be needed following cesarean section to reach the desired analgesic effect.

For the above reasons, further pharmacokinetic studies need to be undertaken to determine the optimal dosing of ketorolac in patients who deliver by cesarean section.

We propose a randomized controlled single blinded trial to compare the morphine milligram equivalents (MME) use in the first 24 hours postoperatively after cesarean section in patients receiving a single dose of 30 mg intravenous ketorolac vs. 60 mg intravenous ketorolac in the operating room after the end of surgery.

2.1 Rationale for a Randomized Controlled Trial

The lack of existing data on optimal postoperative pain management strategy after cesarean section leads to significant variation in management among providers. Use of opioids postoperatively is common in general after major abdominal surgeries including cesarean delivery. Decreasing the use of postoperative use of opioids is of utmost importance, as this category of drugs is known to be addictive. Non-steroidal anti-inflammatory medications such as ketorolac are used as part of postoperative pain management protocols. The optimal dosing of this medication has not been determined especially in pregnancy and peripartum period. However, due to physiologic changes in pregnancy and immediately postpartum and its effects on pharmacokinetics, higher dosage of the medication might be needed to achieve optimal pain control.

To further determine best practice of postoperative pain management after cesarean section, we aim to compare 30 mg IV ketorolac to 60 mg immediately postoperatively.

3.0 Study Design

This is a randomized controlled single blinded trial at The Ohio State University comparing a single dose of 30 mg intravenous ketorolac vs. 60 mg intravenous ketorolac in the operating room immediately after cesarean section.

Potential study participants will be identified at the time of admission to Labor and Delivery unit. Inclusion criteria must be met, namely patient’s age, mode of delivery via cesarean section. The decision for mode of delivery will be at the discretion of the primary OB provider. Indications for cesarean delivery would be: scheduled cesarean due to history of previous uterine surgery including prior cesarean section, failed induction of labor, arrest of second stage of labor, non-reassuring fetal status.

Patients will be approached for consent and enrollment when decision is made to proceed for cesarean section by their primary provider. Patients with allergy to NSAIDs, history of opioid use disorder, chronic pain disorders, or undergoing an emergent Cesarean section, will be excluded from the study.

Once the decision has been made by the primary OB provider to proceed with cesarean delivery, participants will be randomized in to one of two groups:

- Single dose of IV Ketorolac 30mg

Vs.

- Single dose of IV Ketorolac 60mg

The intervention and primary outcome will take place over the span of 24 hour post-cesarean. Once enrolled and randomized, patients will be given either 60 mg or 30 mg of IV ketorolac at the end of the procedure. All other obstetric care will be at the discretion of the primary provider, including but not limited to pain management postoperatively. Analysis will be by intent to treat. The secondary outcomes will be collected during the hospital stay and participants will be followed up to six weeks postpartum.

3.1 Study Aim

The primary aim is to compare the morphine milligram equivalents (MME) use in the first 24 hours postoperatively after cesarean section in patients receiving a single dose of 30 mg intravenous ketorolac vs. 60 mg intravenous ketorolac in the operating room after the end of surgery.

3.3 Secondary Aims

The secondary aims of this study are:

- MME use during the hospital stay
- Patient reported pain score assessment
- Time to first administration of opioid pain medication postoperatively.
- Adverse maternal outcomes (acute kidney injury, admission to intensive care unit, maternal death)
- Type of skin incision (Pfannenstiel vs. Vertical Midline)

3.3 Study Groups

This study is a randomized controlled blinded single center clinical trial conducted at The Ohio State University Wexner Medical Center of pregnant individuals undergoing a cesarean section. These individuals will be consented at the time of decision to proceed for Cesarean section by their primary provider. They will then be randomized at the end of the procedure to receive a single dose of IV ketorolac to one of two groups:

- Single dose of IV Ketorolac 30mg

Vs.

- Single dose of IV Ketorolac 60mg

Participants in the study will have the above regimen administered by the anesthesia team in the operating room in accordance with hospital EMR and policies.

3.4 Population and Eligibility Criteria

a) Setting: This single center study will be conducted at The Ohio State University Wexner Medical Center.

b) Inclusion criteria:

- Pregnant individuals aged 18-45 with a viable single or twin intrauterine pregnancy
- Cesarean section as the delivery mode
- Regional anesthesia (Spinal, Epidural, Combined Spinal Epidural)

c) Exclusion criteria:

- Known allergy or adverse reaction to NSAIDs, aspirin, or ketorolac
- Patients with peptic ulcer disease, preexisting kidney or liver disease
- Individuals at risk for decreased renal clearance (including pregestational diabetic with nephropathy, preeclampsia with severe features, chronic hypertension > 5 years, chronic kidney disease or acute kidney injury)
- Hemodynamically unstable due to hemorrhage
- Acute or chronic pain disorder
- Physician/provider or patient refusal
- Estimated blood loss > 2000 mL
- General anesthesia
- Opioid use disorder
- Emergent Cesarean delivery
- Coagulation disorders
- Active asthma
- Patients weighing <50 kg

3.5 Randomization Method and Masking

Randomization may occur upon confirmation that all inclusion/exclusion criteria are satisfied, after verification of participant consent and HIPAA authorization.

Consenting women will be randomly assigned to single dose of 30 mg intravenous ketorolac vs. 60 mg intravenous ketorolac in a 1:1 ratio according to a randomization sequence. The two study arms are single blinded; with the patient unaware of the treatment assignment.

The simple blocked randomization method will be used to generate the randomization sequences because it provides a high probability of balance in treatment assignments, it is unpredictable, and it allows an explicit randomization analysis to be conducted with relative ease.

3.6 Safety of Ketorolac dosing

Administration of a dose of ketorolac at end of cesarean is routine practice at our institution. There is no established standard dose of ketorolac that we use at our institution. With that said, when giving ketorolac, most providers use a single 30 mg IV dose and some use other dosages such as 15 mg or 60 mg. Maximum daily dose of IV ketorolac per the manufacturer is 120 mg/day. Due to physiologic changes of pregnancy, pharmacokinetic properties of ketorolac may be altered. Pharmacologic activity of ketorolac is associated with its S-ketorolac enantiomer. The clearance of S-ketorolac was found to increase at delivery and peak serum concentration was decreased.[12,13] This suggest that in the period immediately after delivery, a higher dose of ketorolac might be needed to achieve adequate pain control.

There will not be fetal exposure to the medication as it will be administered at the end of the procedure after the baby's delivery. Administration of a dose of ketorolac for postoperative pain management at end of cesarean is routine practice at our institution. Ketorolac can have side effects such as abdominal pain, nausea, or headache. More serious side effects such as peptic ulcers, or gastrointestinal bleeding are rare.

4.0 Study Procedures

4.1 Screening and Eligibility and Consent

The participant's inclusion and exclusion criteria will be verified as will her interest in the study. The informed consent process will be conducted by trained research staff and will include all aspects of the study and a full disclosure of the risks, benefits, procedures, and alternatives. The study consent and HIPAA authorization will be signed after all questions have been discussed and answered. Collection of baseline information, including contact information, demographic and pregnancy history information, will follow the informed consent process. Screening patients in L&D for eligibility will be performed by members of the research team daily during the study period.

4.2 Randomization and Baseline Procedures

Randomization may occur upon confirmation that all inclusion/exclusion criteria are satisfied, after verification of participant consent and HIPAA authorization. Study staff will also verify participant contact information and obtain a Release of Information, as permitted by local policy, to collect outcome and serious adverse event (SAE) documentation. Patients will be assigned next sequential number and ketorolac dose will be determined depending on randomization allocation sequence.

Once the patient is randomized, the patient will receive the medication dose by anesthesia staff in the operating room according to EMR and hospital protocol.

In addition to information collected for eligibility, the following information will be obtained at randomization from a patient interview followed by a review of her chart:

- Demographic information: age, race, insurance status.
- Medical history: pre-pregnancy weight, current weight, height, chronic disease history, allergies.
- Obstetrical history including outcomes of all prior pregnancies if any.
- Social history: marital status, years of education, alcohol use, tobacco use, and maternal drug use.
- Record baseline blood pressure, weight, height and baseline laboratory data including platelets, creatinine, and liver function tests, if performed.
- Medication use e.g. aspirin prior to enrollment, anti-platelet agents, etc..

Opioid use will be converted to equianalgesic doses of morphine sulfate (morphine milligram equivalents [MMEs]) using standard ratios. Table 1 demonstrates opioid conversions.

Table 1. Opioid Conversion Table

Opioid (mg/day)	Conversion factor
hydrocodone 5mg	1

hydrocodone 20mg	1
oxycodone 5mg	1.5
oxycodone 20mg	1.5

Pain scores will be obtained from the patient records. It is standard practice by nursing staff to assess post-operative pain at regular intervals using a 0-10 scale. Total opioid use, time to first opioid use, and pain scores will be extracted from the medical record by members of the research team.

4.3 Obstetric Management and Perioperative care

All aspects of obstetric management will be left to the patient's provider. Routine pre-, intra- and post-operative care will be provided to patients in both groups by their clinical providers.

5.0 Sample Size and Power

Review of inpatient post-operative data, showed that on post-operative day 0 our patients consume on average MME 25 with SD 8. For 20% reduction in MME to 20 and 85% power and type I error of 5% 2-sided, total sample size is 92. Resulting in 46 intervention group (60mg IV) and 46 participants in control group (30mg IV).

5.1 Statistical Analysis Plan

In general, summaries of categorical data will be presented as number of observations and a percentage. Summaries of continuous data will be presented as means with standard deviation if the variable follows a normal distribution, or else as the median and 95% confidence interval.

Binary or categorical will be reported as a proportion with relative risk and 95% confidence intervals as appropriate. For normally distributed continuous outcomes, least squares means general linear regression will be used to estimate means and 95% confidence intervals. For continuous outcomes that are not normally distributed and cannot be transformed to approximate normality, the Wilcoxon test and the Hodges-Lehmann estimators of the median will be reported

Standard comparisons of characteristics between groups will be conducted at baseline. It is anticipated that the randomization scheme will balance the groups for these covariates and they will not be adjusted for in the primary analysis.

The primary analysis will compare MME of the outcome between the 2 study groups. If the two groups show a difference in the primary outcome, interactions will be evaluated and subgroup analyses conducted to determine whether the effect prevails.

Lost to follow up should not occur given study design and no follow up is scheduled. Standard statistical methods for rates and proportions will be appropriate.

6.0 Data Management

6.1 Data Collection Forms

Data extraction from the chart will be performed by trained members of the research team. All data will be de-identified after collection and tracked only with a study ID number.

Data will be collected on standardized forms on which nearly all responses have been

pre-coded. Each form is briefly described below.

- Screening Log
- Eligibility Checklist, including review of prior pregnancy records as applicable
- Randomization: completed for all eligible participants
- Baseline Form: includes detailed demographic and social data, medical & obstetrical history, and current pregnancy complications (to date), as applicable
- Maternal delivery and outcome forms: documents labor, delivery and postpartum information
- Universal adverse event form: documents withdrawal status, side effects since the last dose, or any serious adverse
- Opioid use during hospitalization form: documents time when doses are given, intervals, etc.…

6.2 Recruitment and Data Collection Period

The Ohio State Wexner Medical Center is a large academic medical center with over 5000 deliveries per year. Assuming a 30% rate of cesarean deliveries this is approximately 1500 cesarean deliveries per year. Not every day has 24/7 coverage; therefore it is conservatively assumed that approximately 4 individuals daily are potentially available to enroll on a weekday. It is expected that the number of women who meet the exclusion criteria will be less than 1 percent. Even if 20% of physicians are reluctant to allow their patients to participate (relevant in the setting of private physician deliveries within a hospital) and 60% of individuals refuse consent for the trial, over 360 women could be enrolled annually. Therefore, this study can be completed in less than 1 year.

6.3 Data and Safety Monitoring

A Data and Safety Monitoring Committee (DSMC), a group of individuals affiliated but not listed as PI has been established for this study. The protocol has been approved by them. During the conduct of the study, annually, this group of individuals will monitor the emerging results for efficacy and safety, in addition to protocol adherence. Recommendations by the committee can include protocol modification, early termination for efficacy, or for unexpected safety problems.

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