PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	Prospective Evaluation of the Effects of IV Ketorolac on Platelet Function Post-Cesarean Delivery
Principal Investigator	**John J. Kowalczyk, MD**

B1. PURPOSE OF PROTOCOL

We hypothesize that, compared to placebo, exposure to intravenous (IV) NSAID (ketorolac) impairs platelet function of healthy mothers undergoing elective cesarean delivery.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Cesarean delivery has become the most common surgical procedure in the US, with over 1.2 million cesarean deliveries performed each year.1 The addition of non-steroidal anti-inflammatory drugs (NSAIDs) to a post-cesarean analgesic regimen has been shown to improve the quality of post-cesarean analgesia and markedly reduce opioid consumption.2,3 As a result, fewer patients incur opioid related side-effects such as nausea and vomiting, respiratory compromise, sedation, and impaired breast-feeding.

The effect of NSAIDs on healthy volunteers is relatively well-described.4,5 Most commonly, NSAIDs inhibit membrane-bound cyclooxygenase 1 (COX-1), the enzyme responsible for the production of the platelet agonist thromboxane A2. This ultimately results in inhibition of platelet aggregation and prolonged bleeding time. However, in the obstetric population, the presence and degree of platelet inhibition after NSAID exposure is less clear. This has limited the incorporation of NSAIDs into protocols for postpartum analgesia following cesarean delivery.

PFA-100 assays, with collagen/epinephrine and collagen/ADP as agonists, can reliably test for platelet inhibition.6 PFA has been utilized to examine the anti-platelet effects of platelet inhibitors including NSAIDs in studies involving non-obstetric patients.7-10 Thromboelastography (TEG) has been shown in numerous studies to represent in-vivo clot strength and function.11-16

Research in this field is needed as physiologic changes of pregnancy combined with significant surgical blood loss and hemodilution at cesarean delivery may alter the effect on maternal platelet function. This has become more pressing as postpartum thromboprophylaxis is likely to be more commonly considered for patients after cesarean delivery.17 In their most recent unofficial guidelines, the American Society of Regional Anesthesia state that NSAIDs should not be used with thromboprophylaxis after patients received neuraxial blockade (ASRA App). However, to the best of our knowledge, there is limited data, only utilizing bleeding time,5 examining the potential platelet inhibitory effect of NSAIDs in a low-risk healthy cohort undergoing cesarean delivery.

References:

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B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Study Design

Prospective, randomized, double-blind, placebo-controlled trial.

Endpoints:

Primary outcome: Platelet Aggregometry (ADP-agonist) will be performed before (baseline obtained at completion of the case) and 10 min after IV dosing of study drugs. The timing of the post-dose blood draw was selected because the maximum concentration (Cmax) of IV ketorolac is 2.9 ± 1.8 minutes and known platelet inhibition correlates closely with Cmax.

Secondary outcomes: Platelet Aggregometry (AA-agonist), Thromboelastographic indices (TEG), including R time, K time, alpha angle, and maximum amplitude, TEG platelet mapping MA for AA and ADP, Platelet phosphorylation (pDrp1), laboratory coagulation indices (PT, PTT, INR, fibrinogen). TEG will be perfomed using a Thromboelastography® 6S analyzer (Haemascope Corp. Niles, IL), TEG will be performed before (baseline obtained pre-operatively) and platelet phosphorylation (pDrp1) will be performed by PlateletDiagnostics (Allston, MA). Relevant clinical data will also be collected, including: total estimated blood loss, total volume of intravenous fluid given during the intraoperative period.

Brief Study Protocol

After obtaining IRB approval, patients will be randomly assigned to receive either IV ketorolac 30 mg (n=20) or normal saline (n=20) based on a pre-assigned randomization sequence. The assignment for each patient will be kept in the research pharmacy. After obtaining written informed consent, research pharmacy will provide the team with two syringes, ketorolac and placebo. The vials will be labeled vial A and B. If the patient is assigned to receive ketorolac, syringe A will contain ketorolac and syringe B will contain normal saline placebo. For patient assigned to the placebo arm, syringe A will contain normal saline and syringe B will contain ketorolac. The patient and the study investigators will be blinded to the study drug.

Baseline platelet count, platelet count, coagulation parameters (APTT, PT, Fibrinogen), platelet aggregometry, TEG, TEG Platelet mapping and Platelet phosphorylation (pDrp1) parameters will be measured pre-operatively on the day of surgery. A total volume of 18.9 ml of blood will be withdrawn for the study at this time. Routine lab work obtained at this time will require 10 ml of blood, while study related tests will require 8.9 ml. Each patient will undergo either spinal or combined spinal epidural anesthesia with our standard cesarean induction dose of hyperbaric intrathecal 0.75% bupivacaine 1.5 ml, intrathecal fentanyl 25 micrograms and intrathecal morphine 250 micrograms. 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 be allowed to proceed. The vial A will be administered during skin closure near the completion of the case. Platelet aggregometry, TEG, TEG Platelet mapping and Platelet phosphorylation (pDrp1) parameters will be performed 10 min after study drug administration. While under the effect of the spinal medication, meaning that the patient is unable to fill sharp in their feet, the patient may elect to have this blood and the subsequent blood drawn from their foot to avoid unnecessary pain. These blood draws would only be performed by an anesthesiologist and only if a suitable site were identified. Performing venipuncture for lab draws in the feet is not known to increase the risk of complications from blood draws when compared to the upper extremity. An additional volume of 18.9 ml of blood will be withdrawn for the study at this time. After blood samples have been obtained, patients in each group will receive the vial B containing the alternate therapy (i.e. placebo group receives ketorolac and ketorolac receives placebo),

allowing both groups to benefit from the analgesic effect of ketorolac. Supplemental analgesia will be administered according to a standard post-operative pain management protocol on labor and delivery.

B. Statistical Considerations

Sample Size Justification:

Based on available data from a prior study examining platelet inhibition of non-opioid analgesics,10 a PFA closure time ≥173 seconds can be used to classify platelet inhibition. Using the aforementioned data on epinephrine-induced PFA closure time,10 we estimate that, before and after ketorolac exposure, 25% and 70% patients respectively would exhibit prolonged PFA closure times. With an alpha error of 0.05 and a beta error of 0.8, we estimated that a sample size of 14 patients per group would provide 80% power.

Data Analysis:

Data will be assessed for normality using Q-Q normality plots and the Kolmogorov-Smirnov test. Demographic, obstetric, and perioperative data will be presented as mean (SD) or median [interquartile range]. Between-group comparisons will be assessed using the unpaired t test and Mann-Whitney U test, where appropriate. Within-group before vs. after NSAID exposure changes will be assessed using the paired t test and Wilcoxon signed rank test, where appropriate. The percentage change from baseline for each Platelet Aggregometry, TEG, and lab parameter will also be calculated.

C. Subject Selection

We will study 40 healthy (ASA 1 or 2) women between 18 and 40 years old with singleton term pregnancies undergoing elective, scheduled cesarean delivery with neuraxial anesthesia. Patients will be randomized to receive either IV ketorolac 30 mg (n=20) or normal saline (n=20) before platelet tests. Exclusion criteria are as follows: known allergy or contraindication to NSAIDs, significant medical or obstetrical disease, thrombocytopenia (platelet count < 100 x 10^9/L), history of inherited or acquired coagulation disorder, pre-existing treatment with any of the following drugs: aspirin, NSAIDs, opioids, anticoagulants, and anti-platelet agents.

B4. POSSIBLE BENEFITS

Patients in this study will obtain no direct benefits from participation in the study. Although randomization occurs, due to crossover dosing of patients after blood samples have been obtained, both groups will receive ketorolac for analgesia. This study seeks to better define the degree of platelet inhibition and any possible clinically significant effect for future patients, which may include these patients with subsequent pregnancies.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

This study poses no more than minimal risk to the patient population. Ketorolac and other non-steroidal anti-inflammatory drugs (NSAIDs) added to a post-cesarean analgesic regimen has been shown to improve the quality of post-cesarean analgesia and markedly reduce opioid consumption. They are routinely included in standard orders for many surgeries including cesarean section nation-wide, as well as at this institution. The gained knowledge from this study will define the effect of ketorolac in this patient population, which has not been previously defined, and may be important given the new standard use of anticoagulation for at-risk post cesarean patients.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

Subjects will all be under the study investigators care and study investigators will recruit eligible patients in person during their labor and delivery visit with a physician.

Consent

Once a subject is deemed eligible and agrees to participation in the study, she will meet with a study investigator to begin the informed consent process. No consent will be obtained from patients needing urgent or stat Cesareans, as institutionally defined, in order to ensure that patient have enough time for the consent process and are not in an adverse emotional state at the time of consent. Informed consent will be documented by the use of a written consent form (attached). Each potential participant will have the opportunity to review the consent form with a physician co-investigator to discuss potential benefits and risks of participation. When all questions have been addressed, written consent will be officially obtained. For patients that request additional time to decide on participation, they will be provided with a phone number to call if they desire to proceed. Written informed consent can then be obtained at a subsequent time. All subjects will receive a copy of the signed consent form.

Subject Protection

Consent will be obtained prior to routine, scheduled cesarean section at or around the time of general consent for the procedure. No consent will be obtained from patients needing urgent or stat Cesareans, as institutionally defined, in order to ensure that patient have

enough time for the consent process and are not in an adverse emotional state at the time of consent.

B7. STUDY LOCATION

Privacy

Screening will occur during the normal pre-operative evaluation performed on Labor and Delivery prior to meeting the patient in the pre-operative holding area. Recriutment will be performed in the holding area per standard consent for patients for their cesarean section.

Physical Setting

Consent and all data collection will be performed in the pre-operative holding area. Blood samples will be obtained in the pre-operative holding area, operating room or post-operating holding area, as appropriate.

B8. DATA SECURITY

Initial study documents including consent and enrollment documentation will be stored in the Obstetric Anesthesia office. Study data will be collected and managed using REDCap electronic data capture tools hosted at Beth Israel Deaconess Medical Center. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Identifiable information will be stored in password protected directory accessible only by study personnel. Finally, no identifiable information with be shared outside of BIDMC and all non-identifiable information will be pooled and released as a group for the final study after statistical analysis is complete. Identifiers will be kept until completion of data analysis to allow for review of additional information that may become necessary during the statistical analysis phase. After the completion of the statistical analysis

phase and a sufficient length of time, the file containing the patients' MRNs and study specific unique numerical identifiers will be deleted. No identifiable information with be shared outside of BIDMC and all non-identifiable information will be pooled and released as a group for the final study after statistical analysis is complete. Identifiers will be kept until completion of data analysis to allow for review of additional information that may become necessary during the statistical analysis phase. Patient MRN and unique study specific identifier will be kept until completion of data analysis or <2 years, whichever is greater.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☐ No

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☐ No

N/A - This is not a Multi-Site study.

B10 Dissemination of Research Results

Please explain whether you will be able to thank subjects and provide research results and, if so, how this will be accomplished. If you do not think this is feasible, appropriate or applicable to this research, please specify why.

Patients will be thanked at time of enrollment, however research results will not be routinely distributed to the patients at completion of the study. If a patient specifically requests their individual results or the aggregated results, this will be permitted on an individual basis.