PART B

STUDY DESCRIPTION

TITLE OF PROTOCOL	Dexamethasone vs Ondansetron as the First-Line Antiemetic to Prevent Postoperative Nausea and Vomiting after Cesarean Delivery
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B1. PURPOSE OF PROTOCOL

To determine whether dexamethasone or ondansetron should be used as a first-line antiemetic for prophylaxis against postoperative nausea and vomiting after cesarean delivery. To investigate whether dexamethasone will provide additional analgesic benefit when compared to ondansetron.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Cesarean delivery is the most common surgical procedure performed in the United States, with approximately 1.2 million cesarean deliveries performed in 2020.(1) Cesarean delivery is preferentially performed under neuraxial anesthesia (spinal or epidural anesthesia) to allow mothers to be awake during the delivery of their child and to improve maternal safety. Despite the routine use of neuraxial techniques for most cesarean deliveries in the United States, many patients experience nausea and/or vomiting either during surgery (intraoperative nausea and vomiting, IONV) or after surgery (postoperative nausea and vomiting, PONV).

PONV has traditionally been associated with female gender, history of motion sickness, nonsmoking status, and opioid use.(2) Other authors have shown increased PONV risk with younger age, type of surgery, and general anesthesia as opposed to regional or neuraxial anesthesia.(3,4) Intrathecal opioids, are the gold standard for pain relief after cesarean delivery, and are part of the Society for Obstetric Anesthesia and Perinatology's (SOAP) Early Recover After Cesarean (ERAC) guideline. However, these medications have been implicated in increased rates of PONV.(5) Given the prevalence of cesarean delivery and the importance of maternal well-being, prophylaxis of nausea and vomiting remains an important issue to address.

Medications from multiple classes are commonly administered to prevent and treat PONV after cesarean delivery. These include 5-HT3 antagonists, dopaminergic antagonists, corticosteroids, antihistamines, and anticholinergics. Ondansetron, a 5HT3 antagonist, and dexamethasone, a corticosteroid, are among the most commonly administered medications due to their efficacy and long track record of safety during pregnancy. Indeed, the SOAP ERAC guideline recommends that at least two agents from different classes be administered perioperatively to decrease the rates of IONV and PONV.(6) They further suggest metoclopramide for IONV prophylaxis, ondansetron or dexamethasone for PONV prophylaxis.

The safety and efficacy of ondansetron and dexamethasone are further supported by a 2021 Cochrane Systematic review analyzing medical prophylaxis against IONV and PONV in cesarean delivery.(6) Both ondansetron and dexamethasone decreased postoperative

nausea (Ond: RR 0.45; 10 RCT, 1340 total subjects; Dex: RR 0.59; 6 studies, 733 women) and vomiting rates (Ond: RR 0.47, 10 studies, 1450 women; Dex: RR 0.68; 7 RCT, 793 women). No adverse events from 5HT3 blocking agents or corticosteroids were identified.

Dexamethasone is intriguing as a first-line agent for cesarean delivery since it may have the added benefit of improved pain control and/or decreased postoperative opioid requirement. Several studies have addressed the role of dexamethasone in pain management. A 2008 study by Jaafarpour et al.(8) found a decrease in composite rates of nausea and vomiting, as well reduction of ~1 point on the VAS pain scale for 24 hours following surgery. Data from other studies have been mixed (9, 10, 11).

In conclusion, there is a gap in knowledge in defining the optimal first-line antiemetic for prophylaxis of PONV in patients undergoing cesarean delivery. Our goal is to evaluate the effectiveness of ondansetron vs. dexamethasone on PONV rates and postoperative pain control.

References

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B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Study Design
Prospective, randomized, double-blind, controlled trial.

Endpoints:
Primary outcome: Composite need for treatment of nausea and vomiting, pain, and pruritus in the 24 hours following cesarean delivery.

Secondary outcomes: visual analogue scores for pain, PONV, pruritus in the PACU at 0 and 2 hours, and at 24 hours. Obstetric quality of recovery score (OBQoR-11).

Brief Study Protocol:
Standard care pathway:
Patients will receive standard care for their cesarean and post-cesarean care. This includes preoperative intravenous catheter placement with preoperative IV fluid, standard American Society of Anesthesiologists monitoring, and neuraxial anesthesia (either spinal or combined spinal-epidural) in a sterile fashion. Each patient will receive standard cesarean neuraxial anesthesia dose of intrathecal medication consisting of 1.5 ml of 0.75% hyperbaric bupivacaine, fentanyl 25 mcg, and 150 mcg of morphine. At end of surgery, all patients will receive standard dose of ketorolac 30 mg IV and acetaminophen 1 gm IV and continue with redosing every 6 and 8 hours (respectively) for 24 hours. On arrival to PACU, all patients will receive standard nursing care with standard monitoring of side effects. On discharge from PACU, patients will be transferred to postpartum floor and receive standard nursing care and monitoring.

Over the following 24 hours, all standard post-cesarean medications will be used.
For treatment of breakthrough pain:
- oxycodone 5-10 mg PO every four hours PRN for pain.

For treatment of PONV:
- promethazine 6.25 mg IV as first-line for nausea/vomiting,

- haloperidol 0.5-1 mg IV for refractory nausea/vomiting.

For treatment of pruritus:

- naloxone 0.04 mg IV for refractory pruritus.

Study Procedures:

After induction of spinal anesthesia, patients will receive either dexamethasone 8 mg or ondansetron 4 mg in a randomized and blinded fashion.

Study measurements will all be recorded by a blinded investigator. Patients will be asked to score their nausea, pain, and pruritus on a Visual Analog Scale (10 cm, unmarked line) on arrival to PACU, 2 hours postoperatively, and 24 hours postoperatively. At 24 hours, patients will be asked to complete Quality of Recovery Score following Cesarean Delivery Questionnaire (ObsQoR-11).

The primary outcome is the total rescue medication dose. The incidence of any side effects will be recorded, as will the time to first rescue medications.

B. Statistical Considerations

a. ***Sample Size Justification:***
The sample size for this trial was determine using the two-sample Mann-Whitney U-Test, based on the Alpha (two-sided) = 0.05 and Power = 0.8 with an assumed P(X>Y) 0.67. The required sample size per group is 46. We plan to increase to 50 patients per group to account for drop outs. Thus, we will enroll 100 patients.

b. ***Data Analysis:***

Descriptive statistics of the demographics will be performed. Data will be graphed and assessed for normality using histograms, QQ plots and the Shapiro-Wilk test. Continuous data, such as age, pain scores, and opioid consumption, will be presented as mean (SD) or median [interquartile range], as appropriate. Between-group comparisons will be assessed using the unpaired t-test and Mann-Whitney U test, as appropriate. Categorical data, such as the proportion of patients who successfully completed the study protocol, will be presented as frequencies or proportions and analyzed using a chi-square or Fisher's Exact test. All two-sided p-values ≤0.05 will be considered statistically significant.

C. Subject Selection

All patients will be selected from the schedule or add-on list of cesarean deliveries at BIDMC. All patients will meet inclusion and exclusion criteria.

Inclusion criteria:

- Healthy women (ASA 2)
- Between 18 and 45 years old
- Singleton term pregnancies
- Scheduled or non-labor cesarean delivery
- Neuraxial (spinal or combined-spinal epidural) anesthesia

Exclusion criteria:

- Refusal to participate
- Known allergy or contraindication to any medication used in the study
- Significant medical or obstetrical disease (ASA ≥ 3)
- Antiemetic use within 24 hours preceding cesarean delivery
- Insulin dependent diabetes
- Hyperemesis gravidarum or chronic antiemetic use
- History of daily or near-daily steroid use during pregnancy
- Opioid use disorder or other chronic pain syndrome
- Opioid use during pregnancy
- Use of antipruritus medication, pruritic urticarial papules of pregnancy, or cholestasis of pregnancy

B4. POSSIBLE BENEFITS

All patients in the study will benefit from receiving an antiemetic medication. It is unknown if inclusion in the study will provide additional analgesic benefit to those assigned to the dexamethasone arm. The study will provide benefit to future patients to determine which medication is more efficacious as first-line agent for PONV prophylaxis.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

There are no additional risks for being enrolled in this study as patients would routinely be receiving ondansetron and/or dexamethasone per provider preference. Both medications are routinely administered during cesarean delivery.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

All patients will be identified from the schedule and add-on list of cesarean deliveries at BIDMC. The pateints will be approached by a study investigator who will determine the patient's willingness to participate and if the patient may meet inclusion and exclusion criteria. The investigator will present the study to the patient and perform informed consent for enrollment in the study.

Consent

The study investigator will obtain written informed consent from the potential subject in the preoperative holding area. This is a secure location that is currently used for all medical conversations with patients, including informed consent. The patient's support person(s) (e.g. spouse, parent, etc.) may remain for the informed consent procedure.

Subject Protection

We do not anticipate that any subjects would be vulnerable to coercion or undue influence. No consent will be obtained from patients needing an urgent or stat cesarean delivery, as institutionally defined, in order to ensure that patients have enough time for the consent process and are not in an adverse emotional state at the time of consent. Furthermore, it will be made clear to the patients of the Principal and Co-Investigators that their participation is entirely voluntary and will not affect their clinical care with their physicians if they decline participation. Patients will also have the ability to discontinue their participation at any time.

B7. STUDY LOCATION

Privacy

All conversations will be had in the secured area currently used for private medical conversations. No information will be shared outside of the study personnel and BIDMC. Patient information will extracted from the medical record and entered into a REDCap database. Any paper notes containing patient data will be kept in locked cabinets and rooms.

Physical Setting

All conversations and consent discussions will be help in the preoperative area designed for this type of interaction. The patient will be cared for on the labor and delivery unit for the cesarean delivery, and on the postpartum unit for their recovery. These are the typical locations for these women, whether participating in a study or not.

B8. DATA SECURITY

Initial study documents including consent and enrollment documentation will be stored in the Obstetric anesthesia office in a secured location, accessible to research investigators. Any notes recorded on paper being destroyed in a HIPAA compliant manner.

Research data will be stored on data-encrypted files on a secure server behind the BIDMC firewall. It will be password protected. Only research staff will have access to this data.

Study data will be collected and managed using REDCap electronic data capture tools hosted at Beth Israel Deaconess Medical Center. 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. 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. Data will be destroyed 3 years after publication.

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

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 performed on an individual basis.