A randomized controlled trial on the effects of NSAIDs on postpartum blood pressure in patients with hypertensive disorders of pregnancy

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Background and Rationale: Non-steroidal anti-inflammatory drugs (NSAIDs) are effective agents for the management of pain in the postpartum period.[1,2] The addition of NSAIDs to post-cesarean analgesic regimen has been shown to improve post-cesarean pain and reduce opioid requirements.[1, 3, 4-6]

Concern has been raised over use of NSAIDs in hypertensive pregnant patients, as recent evidence suggests the potential for increased blood pressure in patients with chronic hypertensive disorders receiving these agents. The mechanism by which NSAIDs have been proposed to increase blood pressure is by blocking synthesis of the prostaglandins that regulate vascular tone and sodium excretion. Elevated blood pressure in the immediate postpartum period can lead to adverse health consequences, particularly hemorrhagic stroke,[3,4] as well as pathologic heart remodeling that can lead to long-term cardiovascular morbidity and mortality.[5,6] Persistent postpartum hypertension is also associated with prolonged hospital stays[7] and has the potential to influence patient satisfaction. Therefore, the American College of Obstetrics and Gynecology has suggested that these commonly used postpartum pain relief agents be replaced by other analgesics in women with hypertension that persists for more than 1 day postpartum."[8] However, because of a lack of data, no firm recommendation was provided, no references were provided, and no quality or strength of recommendation was provided in the document.

In fact, limiting use of this analgesic for postpartum women with hypertension may be premature. The suggestion from ACOG was extrapolated from studies conducted on patients with longstanding chronic hypertension, which included males and non-pregnant females. It is therefore unclear whether this recommendation is appropriate for patients with transient hypertensive disorders of pregnancy (HDP). These pregnancy-associated disorders, which include gestational hypertension and preeclampsia, are diagnosed after 20 weeks of gestation and typically resolve by 12 weeks postpartum. Since high blood pressure in these disorders is thought to arise as a result of a complex interplay between maternal and placental mechanisms,[9-12] NSAIDs may not produce similar deleterious effects.

Previous studies on the association of NSAIDs and postpartum blood pressure have been inconclusive. One case report describes a postpartum hypertensive crisis in a patient with preeclampsia with severe features following rectal indomethacin administration.[13] Notably, a recent retrospective study suggested that postpartum NSAIDs were not associated with an increase in blood pressure in women with severe features of preeclampsia.[14] However, limited conclusions can be drawn from this study since it is unclear why some subjects had received NSAIDs and others did not. Therefore, in order to establish if there is a causal link between NSAIDs and elevated blood pressure in hypertensive postpartum women, a prospective trial is necessary.

Currently the use of NSAIDs is not restricted in women with HDP at Miller Children's and Women's Hospital. We propose a double-blind randomized control trial to test the effects of postpartum analgesic medications on blood pressure control in women with HDP. We will also assess postpartum analgesic efficacy and patient satisfaction. With this data, we will be able to evaluate the safety and efficacy of using NSAIDs in the immediate postpartum period in women with HDP.

Study Objectives

This study aims to investigate the effects of ibuprofen on blood pressure in postpartum women with hypertensive disorders of pregnancy (HDP).

Women with HDP are often considered to have a distinct clinical course and risk of adverse outcomes if their hypertension is mild or severe. We will therefore consider these two subgroups as distinct study populations with different primary endpoints.

Specific Aims:

1) In women with severe hypertension prior to delivery, we will compare the incidence of severe postpartum blood pressures in patients receiving ibuprofen versus acetaminophen.

    Hypotheses:
    - There will be no difference in the proportion of women with an episode of severe hypertension in the two study groups.

2) In women with mild hypertension prior to delivery, we will compare average postpartum blood pressure in patients receiving ibuprofen versus acetaminophen.

    Hypotheses:
    - There will be no difference in average postpartum blood pressure between study groups.

Study Population

Potential subjects will be patients admitted for medical care at Miller's Children's and Women's Hospital.

Inclusion Criteria

1. Postpartum females at least 18 years old

2. Delivery occurred at equal to or greater than 24 0/7 weeks gestational age

3. Patient receiving care with the Women's Perinatal Group (Maternal Fetal Medicine practice) or Obstetric Clinic resident services

4. Diagnosis of a hypertensive disorder of pregnancy (HDP), including the following:

- Gestational hypertension
- Preeclampsia without severe features
- Preeclampsia with severe features
- Hemolysis, Elevated Liver Enzymes, Low Platelet (HELLP) Syndrome
- Eclampsia

Exclusion Criteria

1. Diagnosis of chronic hypertension or documentation of elevated blood pressures before 20 weeks gestational age.

2. Renal dysfunction (Serum creatinine measurement >1.3mg/dL during the current pregnancy)

3. Low platelet count (recorded measurement <50,000 during hospital admission)

4. Significant liver dysfunction (AST or ALT >500)

5. Known sensitivities to ibuprofen or acetaminophen

7. Use of therapeutic doses of anticoagulation (low dose anticoagulation used for routine prophylaxis of venous thromboembolism is acceptable)

8. Postpartum hemorrhage requiring transfusion

Subgroups of HDP

Enrollment will be stratified into two groups of hypertensive patients based on the degree of elevation of blood pressures.

- Group 1: "**HDP-Severe"**
    - Patients with at least one severe blood pressure measurement (systolic ≥160mmHg or diastolic ≥105mmHg) prior to randomization will be classified as having a severe hypertensive disorder of pregnancy.
- Group 2: "**HDP-Mild"**
    - Patients without a severe-range blood pressure prior to randomization will be classified as having a mild hypertensive disorder of pregnancy.

The definition of severe hypertension is adopted from the definitions of the American College of Obstetrics and Gynecology[8] and the California Maternal Quality Care Collaborative.

Study Design

An outline of the study design can be found in Appendix I. This study will be a prospective double blinded randomized control trial with participants randomized to receive one of two oral postpartum study analgesic regimens:

- Ibuprofen 600mg every 6 hours
- Acetaminophen 650mg every 6 hours

Participants will be randomized by computer-generated random numbers using consecutively numbered opaque sealed envelopes. The HDP-mild and HDP-severe subgroups will be randomized separately to ensure a balanced number of subjects in these two categories.

Participants will receive the first dose of study analgesic (either oral ibuprofen or oral acetaminophen) no later than 8 hours after delivery, which will be continued until the time of discharge from the hospital. The medication will be offered to the patient every 6 hours, but they will have the option to skip a dose if they prefer. On the other hand, if after taking the scheduled study analgesic medication more analgesic medication is desired, every participant can request additional analgesic medications (i.e. hydrocodone, oxycodone) that are part of the standard options available for postpartum patients at Miller Children's and Women's Hospital.

Blood pressure measurements will be included in the study starting from the time of administration of the study medication until discharge. Blood pressures will be measured at least every 4 hours and recorded in the electronic medical record. Measurements can be taken more frequently, as clinically indicated. Blood pressure cutoffs will be established for physician notification by the RN (see study protocol order set).

Intravenous (IV) antihypertensive medications will be administered according to the previously established management guidelines at Miller Children's and Women's Hospital (see Acute Hypertension Protocol, Appendix II) and the need for such treatment, if any, will be recorded. Oral antihypertensive therapy will be started to treat non-severe hypertension to keep blood pressure <150/100mmHg. Oral antihypertensive medication regimens will be limited to nifedipine and labetalol which are considered first line oral antihypertensive agents for treating postpartum hypertension associated with hypertensive diseases of pregnancy. After initiation of a regimen, subsequent increased dosing of medications will be managed at the treating physician's discretion.

Pain scores will be assessed and recorded at least every 12 hours using visual (Wong-Baker facial grimace scale, Appendix III) or verbal numeric analog scale with scores 1-10 (Appendix IV). Pain measurements can be recorded more frequently as clinically indicated.

A 3-item survey will be administered to patients prior to discharge (Appendix V). The survey will include one item from the HCAHPS survey (Appendix VI), an item to assess patient satisfaction, and an item to assess side effects of the medication. The survey will be administered by research staff and identified with the patient's study ID number.

An interim analysis will be performed for both the "HDP-severe" and "HDP-mild" study groups. The interim analysis will be performed on the primary endpoint when 50% of patients have been randomized and have completed the study including the 3-day outpatient blood pressure check follow-up. The interim analysis will be conducted by an independent group of 2-3 clinicians or researchers in conjunction with the research office who will be blinded to the treatment allocation.

Outpatient Protocol

At the time of discharge, if the patient is being prescribed oral antihypertensive medication as an outpatient, or if she had a blood pressure measurement systolic >140mmHg or diastolic >90mmHg in the prior 24 hours, then she will be advised to avoid ibuprofen as an outpatient. These patients will also receive a prescription for acetaminophen for mild analgesia, as well as additional opioid medications as necessary, with attention to avoiding more than the recommended 4g of acetaminophen from all sources in 24 hours. For example, postoperative patients could be prescribed hydrocodone or oxycodone 5/325 every 4 hours PRN, and acetaminophen 650mg every 8 hours PRN. If every pill is taken in the regimen, the total acetaminophen dose will be 3900mg in 24 hours.

Within 3 days after discharge, the patient will have a visit scheduled at the WPG office or the Obstetric Resident Clinic for a blood pressure check.

Study recruitment for each arm of the study will end when the number of enrolled patients meets the criteria specified by the power analysis for that arm of the study.

Study Procedures

Study Setting

The study will take place at Miller's Women's and Children's Hospital, a tertiary academic community hospital with 6000 deliveries annually.

Patient Identification and Enrollment

Residents, maternal fetal medicine (MFM) fellows, attending physicians, and research coordinators will screen patients for eligibility. The physician members of the team will screen for patients under their direct care, while research staff will review electronic medical records of patients to screen for potential candidates. The patient can be approached about enrollment in the study after admission to the hospital and diagnosis with a HDP. Recruitment will be completed before the initiation of the postpartum order set. Study personnel will be available 24/7 to answer all questions or concerns regarding the study. This team will be available to assist with the study until its completion.

Research coordinators will obtain and maintain data on patient outcomes. All members of the research team will complete the appropriate human subjects research training and provide documentation to the IRB before participating in the study.

Study Protocol Postpartum Order Set

A specific study protocol postpartum order set will be used for all study participants.

The order set will include the following:

- Indication of assigned randomization group (study medication A or B)
- Study drug to be administered every 6 hours, with the first dose prior to 8 hours after delivery
- Vital signs to be recorded every 4 hours minimum per unit standard procedure,
- Management of severe hypertension (defined as systolic BP of $\geq$160 OR diastolic BP $\geq$105 per unit standard protocol as described in the standard Miller's Women's and Children's Hospital acute hypertension order set:
    - Notify MD if systolic BP $\geq$160 mmHg or diastolic BP $\geq$105 mmHg and initiate acute hypertension protocol (Appendix II)
- Pain score assessment at least every 12 hours as per unit policy
- Do not administer NSAID medications
- Do not exceed 1400mg/day of acetaminophen from all sources while on study protocol.
- Any serum creatinine measurement $\geq$1.1 will have serum creatinine measured again at least every 24 hours until the measurement is less than 1.1. A study representative should be contacted.
- Orders for additional PRN pain management:
    - Norco 5/325mg or 10/325mg 1 tab PO q6 hours PRN pain
    - Percocet 5/325mg or 10/325mg 1 tab PO q6 hours PRN pain
    - Additional orders can be activated by the managing physician if needed
        - Hydromorphone 1mg IV q2-4 hours PRN breakthrough pain

- Morphine 5mg IV q2-4 hours PRN breakthrough pain
- Oxycodone 5mg or 10mg 1 tab PO q4-6 hours PRN breakthrough pain

Study Drug Maintenance and Concealment

The pharmacist will individually prepare each dose of the study drug and label it as "study medication A" or "study medication B" with the necessary lot number and expiration date. The study medication will be dispensed as an oral solution to maintain blinding of patients, nursing, and patients. Only the pharmacist will know the identity of study medication A and B. The pharmacy staff will maintain a master inventory with logs of lot numbers and information on the study drug administered to participants.

Randomization

Participants will be randomized by computer-generated random assignments of group "A" and "B". These assignments will be placed in consecutively numbered opaque sealed envelopes. The HDP-mild and HDP-severe subgroups will be randomized separately to ensure a balanced number of subjects in each of these two categories. The physician will indicate the assigned study group "A" or "B" in the study postpartum order set to indicate to pharmacy staff which study medication should be administered.

Data Collection

The following information will be collected for analysis. Please see Appendix VII for the data collection tool.

<u>Patient demographic information:</u>

- Age
- BMI
- Race/ethnicity
- Parity
- Tobacco or substance use in pregnancy
- Pregestational or gestational diabetes

<u>Patient clinical information</u>

- Gestational age at delivery
- IV magnesium use
- Mode of delivery
- Neonatal outcomes: Apgar scores, birthweight, NICU admission

<u>Outcome variables</u>

Outcomes in the HDP-severe subgroup

The primary clinical concern for postpartum patients with HDP-severe is further postpartum episodes of severe hypertension, which are associated with adverse health outcomes such as

cerebrovascular events and seizures. As a result, these patients must be treated with a combination of oral and IV antihypertensive medications to maintain blood pressure control below this threshold. Additionally, the presence of severe hypertension is important because patients cannot be discharged if blood pressures are at this level, which can result in prolonged postpartum hospital stays. By using these endpoints, we will be able to evaluate if there is a difference in these postpartum complications in patients taking ibuprofen or acetaminophen.

Additionally, pain scores will be regularly measured and recorded to assess adequacy of pain control with the two study medications.

Primary outcome for HDP-severe subgroup

Evaluate the incidence of severe blood pressures in women randomized to ibuprofen versus acetaminophen.

- *Null hypothesis*: There is no difference in incidence of postpartum severe hypertension between the two study groups.
- *Primary endpoint*: Proportion of women with at least one episode of severe blood pressure postpartum (systolic $\geq$160mmHg or diastolic $\geq$105mmHg).

Secondary outcomes for HDP-severe subgroup

I. Blood Pressure Measurements

- Total number of blood pressures that are severe-range (systolic $\geq$160mmHg or diastolic $\geq$105mmHg)
- Average MAP using "per protocol" approach (including patients who were treated)
- Average MAP in 24 hour intervals (postpartum day 1, day 2, day 3) and summative over the first 4 days of the postpartum period.
- Outpatient postpartum blood pressure measurement within 3 days after discharge

II. Antihypertensive treatment

- Administration of an antihypertensive medication (yes/no)
- Administration of an acute IV antihypertensive medication (yes/no)
- Administration of an oral antihypertensive medication (yes/no)
    - Need to increase dosing of antihypertensive medication (yes/no)
- Summation of all antihypertensive medications and doses administered

III. Pain control

- Average pain score using numeric analog scale 1-10
    - Visual pain scores with Wong-Baker facial grimace scale will be translated into 1-10 scores
- Use of additional analgesic medications (yes/no)
    - Total number and dosing of analgesic medications
- HCAHPS patient survey at time of discharge
    - "During this hospital stay, how often was your pain well controlled?"
        - Never, sometimes, usually, always

IV. Patient satisfaction/Side effects

- "Were you satisfied with the pain medications you received postpartum?"
  - Definitely no, sometimes, usually, always
- Patient survey for side effects from analgesic medications: GI irritation/sedation
- Length of hospital stay
  - Number of cases where hospital stay in prolonged due to uncontrolled blood pressures

Outcomes in the HDP-mild subgroup

For the HDP-mild subgroup, we are primarily interested in average blood pressure during postpartum stay. Since this group rarely receives antihypertensive treatment, we will be able to isolate the effect of ibuprofen and acetaminophen on average postpartum blood pressure. We will also evaluate if there is a difference in incidence of severe hypertension and need for treatment between the two medication study groups.

Additionally, pain scores will be regularly measured and recorded to assess adequacy of pain control with the two study medications.

Primary Outcome for HDP-mild subgroup

Evaluate average blood pressure in postpartum women randomized to acetaminophen versus ibuprofen.

- *Null hypothesis:* There is no difference in blood pressure between the two study groups.
- *Primary Endpoint*: Average mean arterial pressure (MAP) during postpartum hospital stay.
  - We will exclude any patient who received antihypertensive medications postpartum from this primary analysis

Secondary Outcomes for HDP-mild subgroup

I. Blood Pressure Measurements

- Average MAP using "per protocol" approach (including patients who were treated)
- Average MAP in 24 hour intervals (postpartum day 1, day 2, day 3)
- Incidence and total number of blood pressures that are severe-range (systolic $\geq$160mmHg or diastolic $\geq$105mmHg)
- Outpatient postpartum blood pressure measurement within 3 days after discharge

II. Antihypertensive treatment

- Administration of an antihypertensive medication (yes/no)
- Administration of an acute IV antihypertensive medication (yes/no)
- Administration of an oral antihypertensive medication (yes/no)
  - Need to increase dosing of antihypertensive medication (yes/no)
- Summation of all antihypertensive medications and doses administered

III. Pain control

- Average pain score using numeric analog scale 1-10
    - Visual pain scores with Wong-Baker facial grimace scale will be translated into 1-10 scores
- Use of additional analgesic medications (yes/no)
    - Total number and dosing of analgesic medications
- HCAHPS patient survey at time of discharge
    - "During this hospital stay, how often was your pain well controlled?"
        - Never, sometimes, usually, always

IV. Patient satisfaction/Side effects

- "Were you satisfied with the pain medications you received postpartum?"
  - Definitely no, sometimes, usually, always
- Patient survey for side effects from analgesic medications: GI irritation/sedation
- Length of hospital stay
    - Number of cases where hospital stay in prolonged due to uncontrolled blood pressures

Privacy

Research staff and the investigators will ensure that the consent process, protocol compliance, documentation of CRFs, source document storage, and standards of privacy and confidentiality are maintained throughout the study by the research coordinator and research staff.

Statistical Considerations

The outcome data from the two subgroups of HDP-severe and HDP-mild will be analyzed separately.

Power analysis

I. HDP-Severe Subgroup

The study will be powered to detect a difference in the proportion of patients who have an episode of severe postpartum blood pressure between the two study groups. Based on a prior study of women with preeclampsia with severe features exposed to NSAIDs postpartum, 59% of women require treatment with antihypertensive medications.[9] Another study reported an 88% rate of antihypertensive treatment postpartum in women with HDP, although they did not indicate if NSAIDs were prescribed.[15] We therefore estimate that 75% of HDP-severe patients taking NSAIDs will have at least one severe blood pressure postpartum.

Since NSAIDs have the potential to contribute to postpartum pain control, we anticipate that we would need to demonstrate a large clinical effect on blood pressure in order to influence current prescribing practices. We therefore would like to detect a 35% decrease in number of patients with at least one severe blood pressure postpartum in the acetaminophen study group, to a rate of 49%. With a statistical significance level of 0.05 and power set at 0.80 in a two-sided test, we

will need to enroll 122 participants. To account for potential dropout in our study groups, we plan to enroll 10% more patients, for a total of 140 HDP-severe patients.

II. *HDP-mild patients*

In women with mild HDP, we would like to detect a change in postpartum mean arterial pressure (MAP) between the two study groups. In several studies of non-pregnant patients, NSAID use led to a MAP increase of 4-6mmHg compared to acetaminophen and placebo groups.[10-11] Therefore, to maximize clinical significance, we will aim to detect a difference in MAP of 6 mmHg between study groups. Previous studies have suggested the standard deviation for average MAP during postpartum stay in women with HDP is 7.9mmHg.[9]

Assuming an average blood pressure of 140/90 in mild hypertensive patients, we will predict a MAP of 107mmHg in the NSAID group, and expect to see a 6 mmHg decrease to a MAP of 101 mmHg in the acetaminophen group. By setting statistical significance at 0.05 and power at 0.80 in a two-sided test, we will need to enroll 56 study participants. To account for potential dropout in our study groups, we plan to enroll 10% more patients, for a total of 62 HDP-mild patients.

Data Analysis

STATA 11.0 software

Comparison of mean arterial blood pressure between groups:

- Student's t-test (comparison of means, assuming data is parametric)
- Logistic regression for all postpartum blood pressure measurements as a continuous variable

Comparisons of frequency of severe blood pressures: difference in median frequency between groups, nonparametric distribution.

- Mann-Whitney U test

Difference in pain score median averages, nonparametric data:

- Mann-Whitney U Test

Other categorical variables: use of antihypertensive meds, need to increase antihypertensive medications, patient satisfaction/side effects

- Chi-squared analysis, Fischer's exact test

Schedule of Study Visits

The patients will be scheduled for one outpatient postpartum blood pressure evaluation within 3 days after discharge.

Risks and Benefits Associated with the Study Procedure

Benefits: There are no benefits to the study participants.

Risks: There are no additional risks over standard current care to participating in the study, since both study drugs are routinely administered for postpartum analgesia at Miller's Children's and Women's Hospital, regardless of the diagnosis of hypertensive diseases of pregnancy. The frequency and dosing of these medications are also consistent with the current standard of care at our hospital. These medications are well tolerated, have minimal side effects, and are available over the counter.

If the assigned treatment regimen does not control pain adequately, several alternative pain medications will be available to the participant. However, the patient would not be able to receive the alternative non-narcotic treatment for mild pain control unless they withdraw from the study.

Monitoring Plan

Research staff and the investigators will ensure that the consent process, protocol compliance, documentation of CRFs, source document storage, and standards of privacy and confidentiality are maintained throughout the study by the research coordinator and research staff.

Additionally, storage of all sensitive material will be in a locked file cabinet and there will be no storage of data with protected health information (PHI) on laptop computers. No PHI will leave the LBMMC premises or be transmitted on personal emails.

Research staff will audit the consent binders to assess that all protocols have been adhered to. Study personnel will be available 24/7 to answer all questions or concerns regarding the study.

Safety Considerations

Pharmacy and study personnel will ensure all safety procedures will be maintained throughout the study. If a significant unanticipated adverse event or other unanticipated problem is identified, the investigators or designee will report them within 7 days (if the event is serious) or within 14 days (for any other unanticipated problems) of becoming aware of the problem and records will be maintained in the research coordinator's file. All data will be kept in the research coordinator office, which has a locked door and in a cabinet that is double locked.

Potential complications of high blood pressure during pregnancy include stroke and seizures. Complications from antihypertensive medications include sudden symptomatic low blood pressure. Potential complications from the study medications include gastrointestinal bleeding and renal dysfunction (ibuprofen) and liver dysfunction (acetaminophen), although neither study drug will be administered in the high doses that are associated with these complications. However, as a precaution we will have a serum creatinine monitoring protocol in place. Currently, as part of routine of care, every hypertensive obstetric patient receives a measurement of creatinine (along with liver function enzymes and complete blood count) when admitted to the hospital. If serum creatinine measurement is $\geq$1.1mg/dl, we will monitor creatinine levels every 24 hours until the measurement is less than 1.1mg/dL. A study representative will be contacted to ensure that these levels are monitored appropriately. If the creatinine increases to 1.4 mg/dl or above, the patient will be the study medication will be unmasked. If the patient was assigned to ibuprofen, the medication will be discontinued and this unanticipated problem will be reported to the IRB.

An interim analysis will be performed for both the "HDP-severe" and "HDP-mild" study groups.

The interim analysis will be performed on the primary endpoint when 50% of patients have been randomized and have completed the study including the 3-day outpatient blood pressure check follow-up. The interim analysis will be conducted by an independent group of 2-3 clinicians or researchers in conjunction with the research office who will be blinded to the treatment allocation. The validated Peto approach will be used: the trial will be ended if a significant difference in primary outcomes is found between the two study groups using symmetric stopping boundaries at $p<0.001$. Additionally, the study will be halted if there are significant differences in numbers of patients in each group with serum creatinine that exceeds >1.4mg/dl while using the study drug using symmetric stopping boundaries at $p<0.001$.

Confidentiality

Throughout the study, only study personnel will have access to collected subject data. Please see application for description of who will have access to data. Additionally, storage of all sensitive material will be in a locked file cabinet and there will be no storage of data with protected health information (PHI) on laptop computers. No PHI will leave the LBMMC premises or be transmitted on personal emails.

The data will be collected until the predefined number of patients have been enrolled and completed the study. After the study's closure, the data will be stored for thirty years, and subsequently destroyed.

Please see HIPAA subject authorization form for more details (Appendix VIII).

Appendices:

I. Study design flow diagram

II. Hypertension Protocol

III. Visual Analog Pain Scale

IV. Verbal Numeric Analog Pain Scale

V. Discharge Assessment Patient Survey

VI. HCAHPS Survey

VII. Data Collection Tool

VIII. HIPAA Subject Authorization Form

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