Preeclampsia And Nonsteroidal Drugs for Analgesia (PANDA): a randomized non inferiority trial

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A Introduction

A1 Study Abstract

Recently published clinical guidelines for the care of women with hypertensive disorders recommended that nonsteroidal anti-inflammatory drugs (NSAIDs) should be withheld from patients with hypertension that persists for more than one day postpartum. There has been a paucity of data from the obstetric literature to support or rebuff this recommendation. As the opioid crisis worsens in the United States, additional attention and resources have focused on limiting the use of narcotic medications. The effective employment of non-opioid analgesics has been shown to reduce narcotic use. Ibuprofen and other NSAIDs are the most effective and most commonly prescribed analgesics for postpartum pain, but clinicians now find themselves stuck between these recommendations and their efforts to limit unnecessary opioid prescriptions. We propose a randomized controlled non-inferiority trial of women with preeclampsia comparing a postpartum analgesic protocol that includes NSAIDs, to one that excludes them. Our central hypothesis is that NSAID use does not worsen hypertensive diseases of pregnancy. Our primary aim is to determine the effect of NSAIDs on postpartum antihypertensive requirements.

A2 Primary Hypothesis

Our central hypothesis is that NSAID use does not worsen hypertensive diseases of pregnancy.

A3 Purpose of the Study Protocol

Recently published clinical guidelines for the care of women with hypertensive disorders recommended that nonsteroidal anti-inflammatory drugs (NSAIDs) should be withheld from patients with hypertension that persists for more than one day postpartum (1). This recommendation is based in data from the general medicine literature, which suggests a role of NSAIDs in precipitating hypertension in non-pregnant adults (2,3). It may also draw from previously published case reports of post-partum hypertension that were thought to be NSAID induced (4). There has been a paucity of data from the obstetric literature to support or rebuff this recommendation. As the opioid crisis worsens in the United States, additional attention and resources have focused on limiting the use of narcotic medications. The effective employment of non-opioid analgesics has been shown to reduce narcotic use (5). Ibuprofen and other NSAIDs are the most effective and most commonly prescribed analgesics for postpartum pain, but clinicians now find themselves stuck between these recommendations and their efforts to limit unnecessary opioid prescriptions.

We propose a randomized controlled non-inferiority trial of women with preeclampsia comparing a postpartum analgesic protocol that includes NSAIDs, to one that excludes them. Our central hypothesis is that NSAID use does not worsen hypertensive diseases of pregnancy.

B Background

B1 Prior Literature and Studies

Burden of postpartum hypertension: Hypertensive disorders effect up to 10% of pregnancies. They are a significant contributor to maternal and perinatal morbidity and mortality worldwide. Maternal morbidity from severe hypertension can be significant and potentially life-threatening. Stroke, cerebral hemorrhage, heart failure, pulmonary edema, and renal failure can occur from end organ damage with uncontrolled hypertension. Maternal mortality was attributed to hypertensive disorders in 13% of women in the Confidential Enquiries into Maternal Deaths [2]. Hypertensive disease that originates or persists into the postpartum period contribute to prolonged hospitalizations and hospital readmissions. Presence of these conditions in the peripartum period has also been linked to lifelong cardiovascular risk.

The American College of Obstetrician and Gynecologists Task Force on Hypertension in Pregnancy released guidelines for the clinical care of hypertension in pregnancy in 2013. These guidelines included a statement which suggested that nonsteroidal anti-inflammatory drugs (NSAIDs) should be withheld from patients with hypertension that persists for more than one day postpartum. There are two sources for this recommendation. The first is based in data from the general medicine literature, which suggests a role of NSAIDs in precipitating hypertension in non-pregnant adults. The second may draw from previously published case reports of post-partum hypertension that were thought to be NSAID induced.

Biologic feasibility: There are multiple mechanisms which contribute to a biologic possibility that NSAIDs negatively impact postpartum hypertension. In Vivo studies have demonstrated that NSAIDs inhibit aldosterone and prostaglandin metabolism, potentially worsening vasoconstriction. Nonsteroidal medications produce vasoconstriction of the afferent renal arteriole, reducing GFR, and obstruct sodium excretion, with a combined effect of inhibiting diuresis. Cytochrome-450 induction and Cox inhibition may lead to the accumulation of vasoactive metabolites of arachidonic acid.

Related Research: Recent attention to this clinical question has generated data from multiple retrospective cohorts. Vieri et al found no difference in clinically significant hypertensive episodes in their 399 patients regardless of NSAID exposure. Of note, they also found no difference between rates of renal injury, pulmonary edema, and intensive care unit admission. This replicates the findings of Wasden Et al, who in addition, showed that there were no increased antihypertensive requirements in those who received NSAIDs.

A prospective trial was completed in Panama and published in 2017. Vigil-De Gracia and colleagues randomized women with severe preeclampsia to acetaminophen or Ibuprofen for postpartum pain control. The cohort, limited to women after vaginal birth, showed a statistically higher rate of hypertension (systolic BP>150 or diastolic >100) after the first 24 hour postpartum in those who received ibuprofen. There was no difference in rates of severe range blood pressures (>160/110). This study was limited by its small sample size (n=113), exclusion of those delivered by cesarean section, and open label- randomization.

A double masked, randomized controlled trial completed by Blue et al in 2018, did not replicate these findings. Key results from this study showed no difference in the duration of severe range blood pressures in the ibuprofen vs acetaminophen groups, no difference in mean arterial pressures, need for antihypertensives, or laboratory evidence of end organ dysfunction between the treatment groups. Follow-up was carried out to 6 weeks postpartum, and while 23% of the cohort was lost to follow-up by 6 weeks, the remaining patients showed no difference between treatment groups. The study was designed and powered as a superiority trial. Thus, its findings suggested that acetaminophen is not superior to Ibuprofen, but cannot be used to draw conclusions of equivalence or non-inferiority.

Using internal data, we completed a planned secondary analysis of a prospective cohort study of consecutive term patients meeting diagnostic criteria for preeclampsia with severe features. Ibuprofen dose, frequency and time of administration were collected during the postpartum course. Noninvasive measurements of systolic and diastolic blood pressures (NIBP) were used to calculate daily mean arterial pressure (MAP). Of the 335 patients in our analysis, 94% received Ibuprofen postpartum. For those that received Ibuprofen, there was no association between daily Ibuprofen dose and mean postpartum MAP. The median total dose of ibuprofen was 3g during the post-partum hospitalization. Patients who received more than 3g of ibuprofen had an average MAP of 100.5+9.1 mmHg, which did not differ significantly from those who received less than 3g (99.4+9.4 mmHg, p= 0.28).

Table 1. MAPs postpartum across median ibuprofen dosage group

	Ibuprofen dose > 3g (n=132)	**Ibuprofen dose ≤ 3g (n= 183)**	**P**
Overall mean MAPs postpartum	100.5 ± 9.1	99.4 ± 9.4	0.28
Mode of delivery			
Vaginal	101.0 ± 9.0	99.1 ± 9.5	0.16
Cesarean	100.0 ± 9.4	101.6 ± 7.5	0.49

We then examined the relationship between ibuprofen dose and the need for antihypertensive medications while hospitalized or at time of discharge. In this same cohort, antihypertensive medications were required in 42% of patients postpartum and 33% of patients at time of discharge. Mean total Ibuprofen doses were higher in those who required antihypertensive medication compared to those who did not, but this was not significant after controlling for length of hospital stay and admission BP severity (aOR 1.03, 95% CI 0.92 – 1.15). Those who required antihypertensive medications on discharge did not have a significantly higher mean total Ibuprofen doses while inpatient (aOR 1.06, 95% CI 0.95 – 1.18).

Table 2. Association between ibuprofen dose and blood pressure medications postpartum and at time of discharge

	BP Meds PP (n= 141)	**No BP Meds PP (n= 194)**	**P**	**aOR* (95% CI)**
Ibuprofen dose, mg	3664 ± 2021	2836 ± 1474	<0.01	1.03 (0.92, 1.15)
	BP Meds at Discharge (n= 110)	No BP Meds at Discharge (n= 225)		
Ibuprofen dose, mg	3706 ± 1835	2932 ± 1685	<0.01	1.06 (0.95, 1.18)

*Adjusted for number of days inpatient postpartum, admission MAP

NSAID analgesic effects and opioid use: As the opioid crisis worsens in the United States, additional attention and resources have focused on limiting the use of narcotic medications. The effective employment of non-opioid analgesics has been shown to reduce narcotic use (5). NSAIDs are the most commonly prescribed, and the most effective, medication for postpartum pain (12). Blue et al found no difference in pain scores or opioid use between the Ibuprofen and Acetaminophen groups. To date, there are no randomized controlled trials comparing opioid use in patients with and without NSAID analgesia.

B2 Rationale for this Study

There is currently a paucity of data examining the impact of NSAIDs on postpartum preeclampsia. Safety concerns have led to recommendations limiting their use, but these concerns have not yet been born out in the literature. Retrospective analysis, including from our internal data, have displayed relative safety. These studies are prone to the bias and limitations of any retrospective cohort. The two published prospective trials had conflicting findings and significant limitations. The proposed trial has several features that make it an innovative and unique approach to the clinical question of what role NSAIDs have in postpartum analgesia for patients with preeclampsia with severe features. First, as proposed, this trial would be the largest to date examining this question. Second, our trial is powered and designed as a non-inferiority trial, expanding its potential impact on clinical care. Lastly, this trial is designed to mimic actual clinical practice. Where previous studies have compared acetaminophen alone to Ibuprofen alone, it is the practice at our institution, and we assume many others, to use both acetaminophen and ibuprofen in combination for post-partum analgesia. Our trial is designed to determine the effect of prescribing vs withholding NSAIDs in addition to the standard analgesic care. This becomes important as we understand that acetaminophen is also a COX-2 inhibitor and has some inhibitory effect on prostaglandin synthesis. Findings from this study have potential to impact the over 300,000 births each year effected by preeclampsia. These findings will be vital to establishing the standard of care in these patients, promoting safe analgesia while decreasing opioid use in the postpartum period.

C Study Objectives

C1 Primary Aim

Determine the effect of NSAIDs on postpartum antihypertensive requirements
Hypothesis: Analgesic bundles that include NSAIDS, compared to those that exclude them, are not associated with antihypertensive requirements in the postpartum period.

C2 Secondary Aims

Secondary Aim #1: Characterize the effect of NSAID use on preeclampsia related end organ injury.
Hypothesis: NSAID administration will be associated with a rate of renal and hepatic injury that is not different from those not exposed to NSAIDs.

Secondary Aim #2: Evaluate the effect of NSAIDs on patient perception of pain, and opioid analgesic requirements.
Hypothesis: NSAID administration will be associated with decreased patient perception of pain and decreased use of opioid analgesics.

C3 Rationale for the Selection of Outcome Measures

The expected outcome of this study is high-quality evidence for management of postpartum pain in patients with preeclampsia with severe features to reduce opioid use and improve maternal outcomes. Achievement of the specific aims of the study will thus have an important impact on clinical management of this at-risk patient population and decrease maternal morbidities.

D Study Design

D1 Overview or Design Summary

This will be a randomized noninferiority trial aimed at determining the efficacy of NSAIDs for management of postpartum pain in patients with severe postpartum preeclampsia. The randomized control trial is the 'gold standard' for research design. A case control or cohort study may be limited by selection bias and confounding. Random allocation of patients to interventions will minimize selection bias and confounding by both measured and unmeasured factors. Noninferiority trials test whether a new experimental treatment is not unacceptably less efficacious than a treatment already in use. They are used when the treatment may offer advantages over standard treatments, in terms of improved safety, convenience, better compliance, or cost. This study design requires a larger sample size, and specific statistical analysis, but is required to draw a conclusion such as: NSAIDs are not inferior to other analgesics in their effect on hypertension. We will follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines wherever appropriate in the conduct and reporting of this trial. We will use broad inclusion criteria and computer-generated random sequences to assign participants to the two interventions. Postpartum management will be similar in the two groups except for the analgesics available. Analysis will follow the intention-to-treat principle. The use of broad inclusion criteria and intention-to-treat analysis will allow a more conservative estimate of differences in outcomes between the two regimens and allow a better estimate of effectiveness and public health implications of practice change than would pure estimate of efficacy alone.

D2 Subject Selection and Withdrawal

2.a Inclusion Criteria

Women at > 23 weeks gestational age undergoing vaginal or cesarean delivery at Barnes-Jewish Hospital with:

i) An antepartum diagnosis of preeclampsia with severe features

[Pre-eclampsia with severe features will be defined as elevated blood pressure ≥ 160/110, or pre-eclampsia in the setting of thrombocytopenia (platelet count < 100,000), impaired liver function (AST elevated to twice upper limit of normal) or persistent epigastric pain, renal insufficiency (serum creatinine of 1.1 mg/dl or doubling of prior value), pulmonary edema, or new onset visual disturbance or headache unresponsive to therapy.]

2.a Exclusion Criteria

Women with NSAID allergy, an allergy to acetaminophen, Antihypertensive use in this pregnancy prior to 20 weeks gestation, chronic kidney disease or Acute kidney injury with Creatine clearance less than 60 mL/min, inability to obtain consent, Opioid abuse disorder, or peptic ulcer disease.

2.b Ethical Considerations

As this study addresses issues of analgesia and pain control, ethical considerations are of utmost importance. Pain control in the postpartum period is an important factor in patient perceived autonomy and overall satisfaction with the birthing process. In addition, physician prescribed opiod use has a known association with later opiod abuse disorders. This study has potential ethical considerations for its participants and its future findings have the potential to impact ethical considerations for many poatpartum patient's.

This study will seek to balence concerns for beneficence and nonmaleficence while maintaining patient autonomy. First, out goal is do no harm. The existing data reviewed above in this protocol suggests that NSAIDs are safe in the poastpartum period and that withholding NSAIDs does not increase patient reliance on narcotic medications. Second, our goal is to use the data collected and published from this study to improve patient safety and satisfaction for all women in the postpartum period. Lastly, it is of utmost importance that we protect patient autonomy in this study. Patients will be allowed to exit the study at any time, before or after randomization. We have taken this crossover into account in our power calculations.

2.c Subject Recruitment Plans and Consent Process

We will employ familiar efficient recruitment techniques we have used in recent randomized trials in the same settings. All women admitted to the labor and delivery units of the participating medical centers will be screened against inclusion and exclusion criteria. Eligible subjects will be approached for written consent to participate in the study once they are diagnosed with preeclampsia with severe features.

2.d Randomization Method and Blinding

Although consent to participate will be obtained irrespective of mode of delivery, randomization will be performed only when delivery is complete. This is necessary to allow stratification by mode of delivery and eliminate any bias mode of delivery might introduce into our moderate sample size.

Because of the ethical concerns of blinding patients or providers to analgesic treatments, neither patients nor physicians will be blinded to the group assignment of the subjects. Treating physicians will make decisions on escalation of analgesic medications on a case by case basis, with a goal of maintaining the patient in their treatment group unless they request to end their participation in the study.

2.e Risks and Benefits

The risks associated with study participation are theoretical as they have not been consistently described in the existing literature. There is no clear link between NSAID use and worsening hypetension in patients with preeclampsia, but there is a theoretical risks described in the

introduction above. There is also the known risks associated with Ibuprofen use as described in its FDA approval documentation. These risks include: Cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, Gastrointestinal ulceration, perforation and bleeding, Hypertension, Congestive heart failure and Renal Injury. These risks are described in low rates in chronic Ibuprofen users. Ibuprofen is generally accepted as a safe medication for use in acute pain setting and for treatment of postpartum and postoperative pain.

Benefits of study participation for those enrolled include the benefits of routine postpartum care and analgesia. This includes pain score monitoring and blood pressure monitoring. Compensation of $25 will be provided at the end of participation. Benefits of this work extend beyond the study population as its findings will be applicable to upwards of 15% of postpartum women.

2.f Early Withdrawal of Subjects

Patients will be able to withdrawl from study participation at any time.

2.g When and How to Withdraw Subjects

Patients can withdraw from the study by informing any member of their medical care team. This information will be passed from those team members to the research staff.

2.h Data Collection and Follow-up for Withdrawn Subjects

This study will be completed as an intent to treat analysis. Crossover from one study group to the other, or withdrawl from study in its entirely will be documented so that the already existing data on that patient can be collated appropriately.

D3 Study Drug

3.a Description

Ibuprofen is a Nonsteroidal Anti-Inflamitory Drug (NSAID) used for analgesia in the postpartum and postoperative period. It is an FDA approved medication with excellent patient safety and tolerance data.

3.b Treatment Regimen

Patients will be randomized to one of the following:

1. **Standard Analgesic bundle: Ibuprofen 600mg PO q 6 hrs as needed for pain, Acetaminophen 1000mg q 8 hrs as needed for pain, and Oxycodone 5 to 10 mg q 4 hrs as needed for pain**
    a. **In patients undergoing cesarean section, ketorolac 30mg IV q 6 hrs may be substituted as an IV alternative to ibuprofen for the first 24 hours after surgery**
2. **NSAID free analgesic bundle**: **Acetaminophen 1000mg q 8 hrs as needed for pain, and Oxycodone 5 to 10 mg q 4 hrs as needed for pain**

3.c Method for Assigning Subjects to Treatment Groups

Enrolled patients will be randomly assigned in a 1:1 ratio using computer-generated randomization sequence, stratified by mode of delivery.

3.d Preparation and Administration of Study Drug

As Ibuprofen is a standard medication used in postpartum pain, it will be prepared and administered in the usual fashion. Preparation will be by the BJH pharmacy and administration will be per the Nursing staff.

3.e Subject Compliance Monitoring

Daily review of analgesic protocol adhearance will be performed by the study staff and the labor and delivery clinical pharmacists.

3.f Prior and Concomitant Therapy

Prior therapy will not be considered for this over the counter FDA approved medication. Concominant therapy will not be allowed and will be avoided as all duplicate therapies are monitored for inpatients, by BJH medical and pharmacy staff.

3.g Packaging

As this medication is being used according to its FDA approved role, no additional packaging will be used.

3.h Blinding of Study Drug

This is an unblinded study protocol.

3.i Receiving, Storage, Dispensing and Return

Ibuprofen will be used in accordance with existing BJH pharmacy guidelines. No additional protocols are required for this use.

E Study Procedures

E1 Screening for Eligibility

We will employ familiar efficient recruitment techniques we have used in recent randomized trials in the same settings. All women admitted to the labor and delivery units of the participating medical centers will be screened against inclusion and exclusion criteria.

E2 Schedule of Measurements

We will collect extensive antepartum, intrapartum, and postpartum data up to the 6 week postpartum clinic visit (**Table 3**). Data will be extracted from the medical record by trained research assistants. Surveys will be obtained at the 6 weeks postpartum visit by trained research staff. A CMP will be obtained during the inpatient postpartum period only if clinically indicated to asses renal and hepatic function.

Table 3: Data to be collected
Antepartum Data
• **Demographic characteristics: age, race, tobacco** • **Medical history: diabetes, chronic hypertension, maternal body mass index** • **Obstetric history: gestational age at delivery, pregnancy complications (gestational diabetes, preeclampsia, gestational hypertension)**
Intrapartum Data
• **Labor type (spontaneous, induced, augmented)** • **Labor duration** • **Delivery type: cesarean, instrumental vaginal, spontaneous vaginal** • **Vaginal laceration grade, if applicable**
Postpartum Data
• **MAPs prior to discharge** • **Renal and hepatic function prior to discharge (CMP)** • **Antihypertensive medication requirements prior to discharge** • **Antihypertensive medications at time of discharge** • **Hypertension-related outpatient visits during the postpartum period** • **Hospital readmissions, indication, length of stay on readmission, treatments on readmission** • **Patient reported pain scores while inpatient** • **Opioid requirements while inpatient and at time of discharge** • **MAP at 6 weeks postpartum visit** • **Patient reported pain scores, opioid use and analgesia satisfaction at 6 weeks postpartum**

E3 Visit 1

Visit 1 will be defined as the patient's inpatient admission for delivery until the time of hospital discharge. The data collected during this visit is defined above.

E4 Visit 2

Visit 2 will be the patient's postpartum visit at 6 weeks after delivery. This is a clinically indicated visit and is standard of care for all delivering women in the United States. In person visits that occur in Washington University School of Medicine or Barnes Jewish Hospital outpatient spaces will proceed as typically scheduled and conducted. Enrolled study patients will have their visit augmented by a brief survey administered by study staff via secured tablet. Please see the addendum for a copy of this questionnaire. Patients who do not have follow up scheduled in either of these two clinical spaces will have their survey administered by trained study staff via telephone.

Some subjects may be contacted 12 months following the completion of the follow up survey, if they consent. This contact will be done to collect additional information regarding their medical history, if needed.

E5 Safety and Adverse Events

5.a Safety and Compliance Monitoring

Safety and compliance monitoring will be performed by two separate review systems. Compliance will be monitored at regular intervals throughout patient participation. Monitoring will be performed by the PI, trained study staff and our clinical pharmacy specialist. Compliance will be monitored daily and any compliance issues will be reported to the PI who will assess and address systematic issues. Safety will be monitored by an independent Data Safety and Monitoring Board as described below in section E5.5.b.i.

5.b Medical Monitoring

i Independent Data and Safety Monitoring Board

An independent Data Safety and Monitoring Board is being recruited from within the Department of Obstetrics and Gynecology at Washington University in St. Louis. This board will be made up of three faculty members without direct study interaction or responsibilities. Faculty will include maternal fetal medicine (MFM) specialists, and non MFM personnel. The board will be given direct reports from study staff on adverse events and data accrual. The board will have direct access to deidentified data. The safety review board will meet annually or earlier as indicated by specific adverse events.

5.c Definitions of Adverse Events

Adverse events will be defined as outcomes outside of the typical clinical findings associated with preeclampsia with severe features. This will include rare complications that are known to be risks intrinsic to preeclampsia, but that may be modified in their frequency by study group. This definition should capture both expected and unexpected adverse events. This will include

maternal death, maternal seizure, persistantly uncontrolled hypertension greater than 4 days after delivery, acute kidney injury, and postpartum readmission.

5.d Classification of Events

i Relationship

Associated events will be defined as those that are temporarily related to the study protocol without other explanatory etiologies. Events will be considered Not Associated if the event is temporarily independent of the study protocol and appear to be explained by another etiology.

ii Severity

Adverse events (AEs) will be categorized into the following catagories.

Mild: Transient (<48 hrs) or mild discomfort with no medical intervention or therapy required.
Moderate: Mild to moderate limitation in activity outside of those typically seen in postpartum care. Some assistance or minimal medical therapy required.
Severe: Marked limitation in activity with medical intervention or therapy required.
Life Threatening: Extreme limitation in activity with significant medical intervention required.

iii Expectedness

Defining adverse events as outcomes outside of the typical clinical findings associated with preeclampsia and rare complications that are known to be risks intrinsic to preeclampsia, will capture both expected and unexpected adverse events.

5.e Data Collection Procedures for Adverse Events

Study staff will perform ongoing adverse event collection. Adverse events will be categorized as associated vs non associated and by their severity as defined in sections E5.5.d.i and E5.5.d.ii. In addition to the real time collection and reporting of severe adverse events, patients will be evaluated for any adverse events at the time of hospital discharge and at the time of study visit 2 as defined above. AE forms will be collected for any event.

5.f Reporting Procedures

All adverse events will be reported directly to the PI and separately to the Independent Review Board. Non-serious AE's will under go routine reporting via bianual reports to the Review Board. Any Serious AE will be reported to the PI and Review Board within 72 hours of awareness. Life threatening AEs will be reported within 24 hours of awareness. Serious events will be defined by any AE that includes death, life threatening illness, hospital readmission, or any event that causes persistent or significant disability.

5.g Adverse Event Reporting Period

Adverse events will be collected and reported throughout the study duration from randomization until 6 weeks postpartum.

5.h Post-study Adverse Event

Adverse events that take place outside of the study period, which extends through the entire postpartum period, and 6 weeks after medication administration, will not be collected or reported.

E6 Study Outcome Measurements and Ascertainment

See Table 3 in section E2.

F Statistical Plan

F1 Sample Size Determination and Power

A sample size estimate was performed for a non-inferiority trial with a binary outcome (antihypertensive needed at time of discharge, yes/no). Preliminary data from our retrospective cohort (see **2B**) was used to estimate that 38% of preeclampsia patients require antihypertensives at time of discharge (62% 'success' rate). The non-inferiority limit of 0.2 was selected so that the study could detect any difference between the treatment groups of up to 20% (**Table 5**). This was chosen given the clinical scenario in which NSAID medications have moderate data to support both their safety and efficacy. Calculations used an alpha of 0.025 and a power of 90%. In other words, if there is truly no difference between the NSAID-containing and NSAID-free analgesic bundle, then 286 total patients are required to be 90% sure that the upper limit of a 95% confidence interval will exclude a difference in favor of the standard group of more than 20%. The sample size estimate accounts for a 15% crossover rate.

Table 5. Sample size estimation (Power 90%, α=0.025)

Non-inferiority limit	Detectable rate w/NSAIDs	Detectable rate w/o NSAIDS	Sample size
10%	56%	62%	1142
20%	50%	62%	286
30%	44%	62%	130

F2 Interim Monitoring and Early Stopping

Given the short duration of this study, the only interim monitoring that will be performed is safety monitoring as described in section 5e. There is no plan for interim analysis and thus no plan to terminate the study early.

F3 Analysis Plan

Comparisons will be made between the two treatment groups in an intention-to-treat analysis. Objective markers of hypertension and its sequelae will be recorded and coded by trained

research staff. Subjective reports of pain perception and analgesia satisfaction will be collected and compared.

F4 Statistical Methods

Data analysis will adhere closely to the Consolidated Standards of Reporting Trials guidelines. Analysis will follow the intention-to-treat principle in which subjects will be analyzed in the group to which they were randomized, regardless of whether or not they received the assigned intervention. This is important because analysis according to the intention-to- treat principle is accepted as the most unbiased assessment of the true therapeutic benefits of a treatment.

We will first employ descriptive statistics to characterize the group of individuals recruited and to investigate comparability of the two groups at baseline. Formal statistical testing will be limited to selected baseline characteristics considered to be prognostic factors for the primary outcome such as mode of delivery, antepartum blood pressures, and presence or absence of chronic hypertension. The Chi-squared or Fisher's exact tests will be used as appropriate to compare the primary outcome (proportion of subjects requiring antihypertensive medications at discharge) and other categorical secondary outcomes and prognostic factors between trial groups. Relative risks and confidence intervals associated with the primary and categorical secondary outcomes will be calculated and reported. Distribution of continuous prognostic factors and secondary outcome measures will be assessed by visual inspection of histograms and the Kolmogorov-smirnov test. Normally distributed variables will be compared by using the two-group independent t-test. If variables are not normally distributed, the Mann-Whitney U test will be used to make comparisons between the trial groups

F5 Missing Outcome Data

Missing outcome data will be coded as missing at the time of data collection. Patient with missing data will remain in the study given our analytic plan of intention to treat. The statistical methods noted in section F4 will be used to account for missing data and minimize their effect on type I and type II error.

F6 Unblinding Procedures

This is an unblinded trial.

G Data Handling and Record Keeping

G1 Confidentiality and Security

Participants will be recruited and consented in a private exam room on the Labor and Delivery floor of Barnes Jewish Hospital. Study follow up will take place in Washington University School of Medicine or Barnes Jewish Hospital outpatient spaces, in a private room. If a subject cannot return to the clinic for the 6 week follow up, the survey will be conducted via phone. The research staff will call from a private office setting in a research area. Study IDs will be provided to each subject to further protect their privacy.

For confidentiality, only members of the research team will have access to the study information. Any information collected will be coded using the unique study ID. The master list that links the study ID to the participant will be kept separately from the research documents and will only be available to research staff.

G2 Training

Research staff are CITI trained, and well versed in conducting clinical research and HIPAA compliance.

G3 Case Report Forms and Source Documents

All paper documents will be stored in a locked drawer in a locked office of the study PI. Access will be limited to only members of the research team.

The master list that links the patient ID to the name of the subject will be kept separate from the study documents. Electronic data will be stored in a REDCap database, which is WU approved, HIPAA compliant, and requires a unique password to login. All electronic work will be done on WU computers, which are encrypted, firewall-protected, and password protected. Only research team members will be able to access electronic data.

G4 Records Retention

Hard copies will be stored in a locked drawer in a locked office of the study PI. We will store these records per the HRPO guidelines consistent with research. Electronic data will be stored in a REDCap database, which is HIPAA compliant and accessible only by unique password login.

H Study Administration

H1 Organization and Participating Centers

This is a single center trial, with all inpatient clinical care taking place at Barnes Jewish Hospital and all outpatient care taking place at Barnes Jewish Hospital and Washington University School of Medicine Center for outpatient Health.

H2 Funding Source and Conflicts of Interest

This trial will be funded by departmental research funds. This does not preclude the possibility of grant funding in the future. Any applications for grant funding will be updated immediately with the Insitutional Review Board.

H3 Subject Stipends or Payments

Patients will be compensated a total of $25 at the completion of their study participation.This compensation will come in the form of a gift card to local merchants.

H4 Study Timetable

Project Period	0-3 months	3-6 months	6-9 months	9-12 months	12-15 months	15-18 months	18 -21 months	21-24 months
ACTIVITIES								
Protocol Development	x							
Trial registration	x							
Staff recruitment and training	x							
Study forms and database	x							
Subject recruitment		x	x	x	x	x	x	x
Data collection & management		x	x	x	x	x	x	x
Data analysis								x
Drafting of manuscript & reports								x
MILESTONES								
Protocol & IRB finalized	**x**							
Recruitment start		x						
50% recruitment				x				
75% recruitment						x		
100% recruitment								x
Data analysis complete								x

I Publication Plan

After completion of this trial and data analysis, we will publish our findings in a peer reviewed medical journal.

J Attachments

J1 Informed consent documents

J2 Questionnaires or surveys

K References

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