Furosemide for Accelerated Recovery of Blood Pressure Postpartum: a randomized controlled trial (FoR BP trial)

A randomized, double-blind, placebo-controlled single center investigation of furosemide's effect on postpartum blood pressure control in pregnancies affected by hypertensive disorders of pregnancy

Protocol date: July 19, 2018

NCT#03556761

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Principal Investigator: Lisa D. Levine, MD, MSCE
Assistant Professor
Division of Maternal Fetal Medicine
Department of Obstetrics and Gynecology
3400 Spruce St
2 Silverstein
Philadelphia, PA 19104

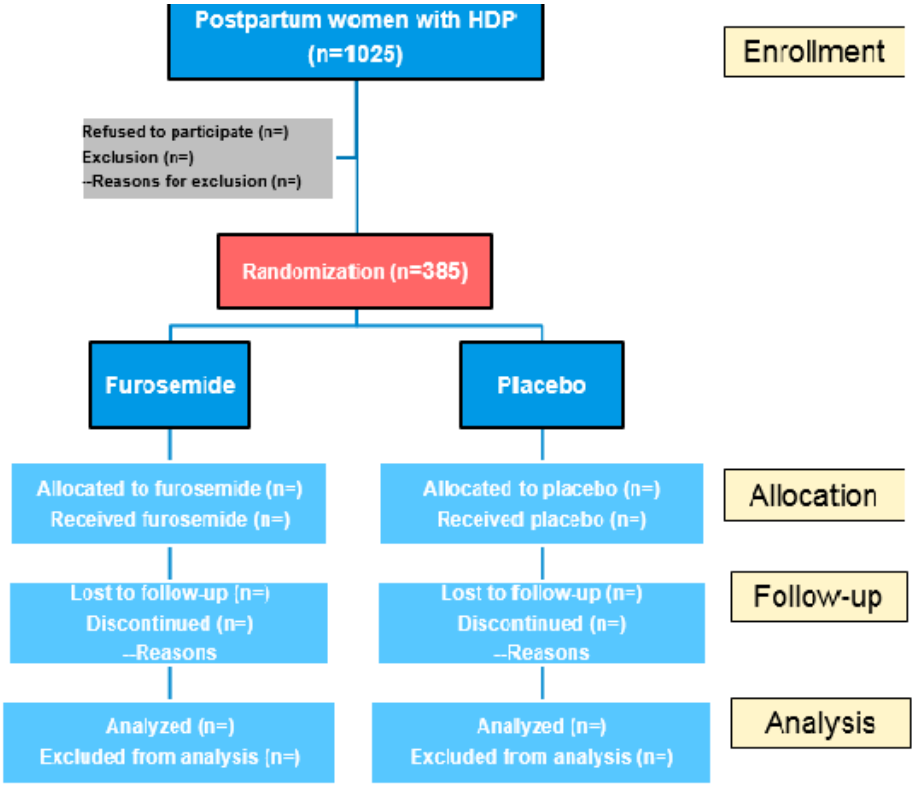
Sub-Investigator(s): Joana Lopes Perdigao, MD
Clinical Fellow
Division of Maternal Fetal Medicine
Department of Obstetrics and Gynecology,

Study Drug/Study Device: Furosemide (Lasix)

LIST OF ABBREVIATIONS

AE	Adverse Event
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
gHTN	Gestational hypertension
H&P	History & Physical Exam
HRPP	Human Research Protections Program
HDP	Hypertensive disorders of pregnancy
HTN	Hypertension
IV (or iv)	Intravenously
PI	Principal Investigator
PO	per os/by mouth/orally
PPHTN	Postpartum hypertension
PR	Partial Response
SAE	Serious Adverse Event

STUDY SCHEMA



STUDY SUMMARY

Title	Furosemide for Accelerated Recovery of Blood Pressure Postpartum: a randomized controlled trial
Short Title	FoR BP trial
Methodology	Double blind, randomized, placebo control design
Study Duration	20 months
Study Center(s)	Single-center
Objectives	To investigate the impact of a short course of furosemide on postpartum blood pressure recovery in women with hypertensive disorders of pregnancy (HDP).
Number of Subjects	385
Diagnosis and Main Inclusion Criteria	Clinical disease state under study: hypertensive disorder of pregnancy, postpartum with delivery >20 weeks EGA, diagnosis of HDP antepartum, intrapartum and up to within 1 day of delivery
Study Product(s), Dose, Route, Regimen	Furosemide (Lasix), 20mg, PO, daily
Duration of administration	5 days
Reference therapy	Placebo
Statistical Methodology	Intention to treat analysis, chi-square tests for categorical variables, two-sample t-test for continuous variables

1 BACKGROUND AND RATIONALE

1.1 Disease Background

Hypertensive disorders of pregnancy are recognized causes of significant maternal/fetal morbidity and mortality, accounting for approximately 18% of maternal deaths worldwide. [1] While significant research has been done on the evaluation and management of hypertension during pregnancy, studies of postpartum hypertension (PPHTN) are usually limited by their retrospective design and focus on inpatients in the immediate postpartum period (2-6 days), or patients who were readmitted due to complications related to hypertension.[2] Few studies have investigated the incidence and proper management of hypertension in the postpartum period. PPHTN can present either *de novo*, following a normotensive pregnancy, or as persistent hypertension following a pregnancy complicated by preeclampsia or other hypertensive disorders of pregnancy.[2,3] Limited information is available on the clinical sequelae of PPHTN, but retrospective studies suggest that it can lead to death or to potentially life-threatening complications, such as cerebrovascular accidents,[4,5] seizures,[6] congestive heart failure, pulmonary edema, and renal failure.[2,7] Furthermore, in the United Kingdom, a review of maternal deaths determined that 10% were related to HDP in the postpartum period.[8] Postpartum hypertension is also the cause of approximately 27% of readmissions to the hospital.[9] These studies clearly show that PPHTN is associated with significant morbidity and that it is important to develop interventions that can reduce its effects.

Guidelines from national organizations such as the American College of Obstetrics and Gynecology (ACOG) recognize the growing concern with postpartum hypertension and have put forth specific guidelines on how to monitor for hypertension postpartum. This includes educating patients of signs and symptoms of pre-eclampsia, monitoring blood pressures for 72 hours in the hospital prior to discharge, and checking an ambulatory blood pressure within 10 days of delivery.[10] However, only checking blood pressures 7 to 10 days after delivery is likely missing a significant number of patients. Several studies note that only 28 to 57% of patients PPHTN have their blood pressure normalize within 3 days[12,13] Furthermore, data out of our own institution noted that 6% of women with HDP were readmitted within 3 to 14 days for hypertension related reasons.[11] Therefore, interventions to improve the care of women with PPHTN are urgently needed.

1.2 Study Agent(s)/Devices Background and Associated Known Toxicities

Furosemide (Lasix) is a loop diuretic that is also a known antihypertensive. It exerts its mechanism of action by inhibiting reabsorption of sodium and chloride in the ascending loop of Henle and distal renal tubule. It also interferes with the chloride-binding cotransport system. Accordingly, this causes increased excretion of water, sodium, chloride, magnesium, and calcium. It is known to have onset of action of up to 60 minutes if given by mouth and 5 minutes if given by IV for diuresis. Duration is estimated to 6-8 hours when given orally and 2 hours when given IV. It is a hepatically metabolized medication with 91-99% protein binding (mostly albumin). Bioavailability ranges from 47-64% orally and it has a half-life of 0.5–2 hours. Excretion is through the urine with 50% of the PO version 80% of the IV version of the drug excreted within 24 hours. Significant side effects are related to the fluid and electrolyte shifts that occur with its lack of resorption of electrolytes. These include, but are not completely limited to ototoxicity, mood changes, confusion, muscle pain, palpitations, dizziness, syncope, increased thirst, fatigue, weakness, decreased appetite, dry mouth, dry eyes, upset stomach, nausea, and emesis.

Prior studies for the prevention and treatment of postpartum hypertension with furosemide had mixed results. Three trials (390 women) assessed oral furosemide (20-40 mg/day) in postpartum women with preeclampsia.[3] In one study, there was a non-statistically significant trend to more rapid blood pressure reduction in the group receiving furosemide.[14] The second study showed that furosemide, given postpartum, was associated with reduced systolic blood pressures only among women with severe preeclampsia.[15] Meanwhile, the third study found that although furosemide was able to reduce the amount of antihypertensive medication given, no significant differences in

blood pressures were found in patients with severe preeclampsia.[16] Given the inconclusive results and little data thus far on the use of postpartum furosemide, a recent Cochrane review concluded that more data is needed on substantive outcomes before the practice of postnatal furosemide can be recommended.[3]

Placebo will be given to half of our enrolled patients which will be determined through randomization. All placebo will be manufactured and distributed by the Investigational Drug Service (IDS) of the University of Pennsylvania. IDS will manufacture the placebo to be similar to the furosemide pill. If necessary, IDS will add a coating shell to both the furosemide and placebo pills to ensure that all pills look similar.

1.3 Rationale

In patients with HDP, postpartum blood pressure has been shown to decrease in the first 48 hours postpartum only to then increase in days 3-6 postpartum.[17-19] This phenomenon is thought to be secondary to large fluid shifts, both secondary from fluid retention during the pregnant state as well as from fluids given intrapartum. Furthermore, large volumes of sodium are also mobilized into the intravascular compartment at this time.[3] Given the latter, furosemide, a loop diuretic that mobilizes sodium and fluid excretion has been posed as a method to prevent severe range blood pressures and their associated maternal morbidity in the postpartum period.

2 STUDY AIMS

2.1 AIM 1: To compare the rate of persistently elevated blood pressures 7 days postpartum in women that receive a five day furosemide course compared to those that receive placebo

2.2 AIM 2: To compare the time (days) required to achieve a resolution of elevated blood pressure.

2.3 Endpoints

2.3.1 Primary endpoint

2.3.1.1 Postpartum hypertension composite outcome, defined as:

- Persistently elevated blood pressure (≥140/90) at 7 days postpartum OR
- Additional requirement of antihypertensive agents after randomization

2.3.2 Secondary endpoints

2.3.2.1 Number of readmission/ ER visit that is hypertension related

2.3.2.2 Frequency of severe hypertension (SBP≥160mmHg or DBP≥110mmHg)

2.3.2.3 Number of days required until blood pressure resolution (<140/90 for 2 days)

2.3.2.4 Postpartum length of stay

2.3.2.5 Complications during hospitalization related to hypertensive disorders of pregnancy (acute pulmonary edema, acute kidney injury, disseminated intravascular coagulation, stroke or myocardial infarction, eclampsia, ICU stay, maternal death)

2.3.2.6 Adverse effects secondary to furosemide

3 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be enrolled to the study. Study treatment may not begin until a subject is consented and randomized.

3.1 Inclusion Criteria

3.1.1 Hypertensive disorder of pregnancy diagnosed antepartum or intrapartum

- Patients with diagnosis of preeclampsia with severe features, superimposed pre-eclampsia and gestational hypertension as diagnosed per ACOG guidelines[10]

    - Gestational hypertension
        - Two blood pressures at least 4 hours apart **≥** 140/90 with no proteinuria or other laboratory abnormalities (detailed below)

    - Pre-eclampsia with severe features and superimposed pre-eclampsia (any of the findings below)
        - Two blood pressures at least 4 hours apart **≥** 160/110 (unless patient given antihypertensive therapy before this time)
        - Thrombocytopenia (platelets <100,000/microliter)
        - Liver enzymes at least twice the normal concentration, and/or severe right upper quadrant/ epigastric pain
        - Serum creatinine > 1.1 mg/dL or a doubling of baseline serum creatinine
        - Pulmonary edema
        - New-onset cerebral or visual disturbances (headache, blurry vision)

3.1.2 New diagnosis of HDP within 1 day from delivery

3.1.3 Postpartum, delivery ≥ 20 weeks EGA

3.1.4 Age ≥18 years old

3.1.5 Have a phone with texting service and be willing to enroll in HUP's established postpartum hypertension texting program, HeartSafe Motherhood

3.1.6 Ability to understand and the willingness to sign a written informed consent and comply with study procedures

3.2 Exclusion Criteria

3.2.1 History of allergic reaction to furosemide

3.2.2 High risk comorbidities for which treatment may be indicated or contraindicated: class C or higher diabetes mellitus, chronic kidney disease or baseline creatinine >1.2, cardiac disorders including cardiomyopathy, congenital heart disease, angina or coronary heart disease, rheumatic disease (lupus), sickle cell disease

3.2.3 Baseline labs with K <3

3.2.4 Use of furosemide or other diuretics antepartum or intrapartum

3.2.5 Use of ototoxic agents including aminoglycosides (ie, Gentamicin for >1 dose), cephalosporins (ie Ancef >1 dose),

3.2.6 Patient unstable for protocol per investigator's judgement

3.3 Vulnerable patient populations

Pregnant women are considered a vulnerable population. As the condition of interest is a pregnancy-related and specific condition, it is unavoidable to exclude pregnant women from this research study. However, all risks to this vulnerable population will be minimized as most of the study will occur in the postpartum period. None of the study medications will be given until the patient has been postpartum for at least 6 hours.

Furthermore, neonates are considered a vulnerable population. We will be collecting data on neonatal rates on NICU admission or readmission to the hospital within 6 weeks postpartum to determine if there are any adverse effects of furosemide to the neonates. All risks to this vulnerable population will be less than minimal risk as furosemide has been used in lactating mothers previously with no neonatal adverse events noted at HUP. Also, no data currently exists in the literature to suggest that furosemide would pose any risk to breastfed infants.

3.4 Ensuring Necessary Medical Interventions

Being enrolled in this study will not change patients' clinical care in regards to antepartum course or delivery decisions. Their intrapartum management will not be different in any way. Regardless of randomization, the management will not be different in either arm apart from whether the intervention medication is given or not. Any elevations of blood pressure postpartum to greater or equal to 150/100 mmHg will receive amlodipine as first-line as an antihypertensive. Patients will be provided with prophylaxis against seizures and deep vein thrombosis appropriately as dictated by clinical care.

3.5 Potential Benefit to Participants

The potential benefit will be prevention of elevation of blood pressures to levels that are associated with high maternal among individuals randomized to the intervention arm. This will lead to a possible increased reduction in hypertension related morbidity, improved patient outcomes, and possibly decreased need for readmission or emergency room visits as compared to placebo. All efforts will be taken to minimize the risks associated with this study and the risks overall are considered minimal; therefore, the risk to subjects is reasonable compared to the benefit to patients and to society in general.

4 TREATMENT PLAN

4.1 Treatment Dosage and Administration

4.1.1 Oral furosemide 20 mg/day OR placebo for a total of 5 consecutive doses.

- Missed or vomited doses will be noted and attempts made to provide them immediately when recognized for missed doses when inpatient. After discharge, patients will be instructed to take a dose as soon as possible if they have missed one. Furthermore, in the unlikely event that patients are discharged without a supply of their medications, we will ensure that the medication will be shipped to their house within 24 hours**.**

4.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to development of ototoxicity or symptomatic derangements in electrolytes as determined by symptoms and corresponding daily basic metabolic profiles. In the event of the development of either, the medication will be discontinued.

4.3 Concomitant Medications/Treatments

To maintain adequate blood pressure control postpartum (goal SBP < 150 mmHg and DBP < 100 mmHg) additional antihypertensive medications may be necessary, and should be used at any time in the postpartum period regardless of enrollment time and first study drug administration:

1) Any patient with persistent postpartum blood pressures, ≥150 mmHg systolic and/or ≥100 mmHg diastolic, will be started on 5 mg of amlodipine PO regardless of study arm or whether they are already taking another antihypertensive maintained from their antepartum period.

2) Any patient with persistent postpartum blood pressures, ≥160 mmHg systolic and/or 100 mmHg diastolic, will be started on 10 mg of amlodipine PO.

3) If blood pressures are still higher than the stated goal above, providers should utilize additional non-diuretic antihypertensive* medications known to be effective in managing elevated peripartum blood pressures.

*Providers will be asked to use non-diuretic medications first, however, if deemed medically necessary, furosemide will be allowed any time in the postpartum period. All uses of diuretic use for medically necessary reasons after enrollment of patient into the trial will be noted.

4.4 Duration of Therapy

Therapy with furosemide will continue daily for 5 days unless there is the development of intercurrent illness that prevents further administration of treatment, unacceptable adverse events, patient withdrawal from the study, or general or specific changes in the patient's condition render continued treatment unacceptable.

4.5 Duration of Follow Up

Patients will be followed for 10 days after discharge. All patients that consent to the study will be expected to enroll at an established program at the Hospital of the University of Pennsylvania to monitor blood pressures postpartum through daily texting. Patients will be expected to measure their blood pressures at least once daily and text them to a physician through the program. The program, Heart Safe Motherhood, has been utilized successfully over the past year to follow-up women after discharge and be more readily available to monitor blood pressures and give advice. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.6 Removal of Patients from Protocol Therapy

Patients will be removed from therapy when any of the criteria listed in Section 4.2 and 5.5 apply. The Principal Investigator will be notified and document the reason for study removal and the date the patient was removed in the Case Report Form. The patient will be followed-up per protocol.

4.7 Management of blinding

This is a double blind study and therefore physicians, staff, and patients will be blinded to the patient's allocated treatment group. In the event of a potential suspected unexpected serious adverse reaction, unblinding will be undertaken by the PI. Unblinding may also be performed at the request of a senior clinician responsible for the care of a trial participant but such requests are likely to occur only in the case of an adverse clinical event and are expected to be rare. Any request to unblind treatment allocation for clinical reasons will be made directly to IDS and the treatment allocation will be reported to the relevant clinician. The PI and main trial manager will be kept informed of all instances of unblinding but remain blind to treatment allocations themselves wherever possible. All requests for unblinding will be recorded by research staff and IDS.

5 STUDY PROCEDURES

5.1 Screening for Recruitment and Recruitment Process

The labor and delivery board and patient list will be screened daily to identify eligible patients. Women identified as having a hypertensive disorder of pregnancy will be invited to participate in the study and written informed consent will be obtained from those who choose to participate in the postpartum period. All screening procedures must be performed within 24 hours of delivery. The screening procedures include:

5.1.1 *Informed Consent*

5.1.2 *Medical history*

Complete medical and surgical history

5.1.3 *Demographics*

Age, gender, race, ethnicity

5.1.4 *Review subject eligibility criteria*

5.1.5 *Review previous and concomitant medications*

5.1.6 *Physical exam including vital signs, height and weight*

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.7 *Adverse event assessment*

Baseline adverse events will be assessed. See section 6 for Adverse Event monitoring and reporting.

5.2 Randomization

If the patient is eligible, after informed consent the patient will be randomized by IDS. We plan to randomize through a computer generated sequence in blocks of 4 and stratify randomization blocks by whether severe features are present or not (ie., gestational hypertension and pre-eclampsia without severe features vs. pre-eclampsia with severe features). IDS will then dispense the furosemide or placebo accordingly.

5.3 Procedures During Treatment

After enrollment and consent, a specific order will be placed in the electronic medical record for this study's purposes. This order will alert IDS that a patient has been enrolled and the patient will be randomized accordingly. After randomization, IDS will send to the floor either 5 doses of placebo or furosemide clearly marked for the specific patient. A research coordinator will be present at this time and ensure that there are 5 doses of furosemide/placebo and that the patient's nurse is aware that the patient is enrolled in the study. The research coordinator will also ensure that the medication order is given by postpartum day 1 and ensures that the first pill is given after 6 hours from delivery. Patients in the furosemide arm will be assigned to receive oral furosemide 20 mg/day for a total of 5 consecutive days during hospitalization and after discharge. This dose of furosemide is based on prior studies,[3] which have shown it to be safe with breast feeding.[2]For those randomized to the placebo group, they will be given placebo pills for a total of 5 consecutive days. The time of initiation of first pill given will be recorded by the research coordinator. Each time a pill is given in the hospital, it will be accounted for in the medical administration record (MAR) in the EMR. Pills should be given approximately 24 hours apart, and the Epic order placed after enrollment will have this distinction.

Patients in both groups will undergo similar postpartum surveillance, including blood pressure and pulse assessment every 4 hours and urinary output measurements while hospitalized. Proper treatment for elevated blood pressures will be initiated immediately as soon as the elevated blood pressures are recognized, and will not be delayed for any study purposes including study drug administration. For this study, antihypertensive therapy will be initiated for persistently elevated postpartum blood pressures (BP) of $\geq$ 150 systolic or $\geq$100 mg Hg diastolic with 5 mg of amlodipine PO. Persistent severe range blood pressures (BP $\geq$160 mm Hg systolic or $\geq$110 mm Hg diastolic) will be treated with IV antihypertensives if needed, as well as 10 mg of amlodipine PO. If further antihypertensive medications are needed to maintain blood pressures <150/100, these will be per the discretion of the clinical staff in both arms. All physicians and clinical staff in Labor and Delivery as well the postpartum unit will be educated extensively to avoid diuretic antihypertensive medications unless deemed medically necessary. Furthermore, diagnostic and laboratory tests will be per the discretion of the clinical staff in both arms as well. Routinely, all patients undergoing cesarean section remain hospitalized for at least 3 days and all patients with preeclampsia with severe features are kept in the hospital for 3 days (per the recommendations of the ACOG Task Force on Hypertension in Pregnancy).[10] All patients will be followed at for 10 days after discharge as detailed below. Being enrolled in the study will not change the patient's clinical care at any time. Physicians, staff, and patients will be blinded to the intervention administered, unless a break in blinding is required for medical intervention of adverse effects.

5.4 Follow-up Procedures

Prior to patient discharge, a research coordinator will ensure that the patient has the correct amount of pills left and will review instructions about taking the pill daily for however many remaining doses there are. If patients are breastfeeding exclusively, the

research coordinators will ask the patients upon discharge if they encountered any difficulties with breastfeeding while in the hospital. Patients will be followed for 10 days after discharge through Heart Safe Motherhood, a texting program offered at the Hospital of University of Pennsylvania in which women with HDP take their own blood pressures at home, and report those blood pressures through a texting service. A physician who is part of the study, will review the blood pressures daily and notify patients if more blood pressures, medications, or medical attention are needed. All patients in the study will be asked to text through the program their daily blood pressure and an affirmation that they are taking the remaining daily doses of furosemide/placebo at home. All patients, regardless of whether they are in the study or not, are expected to have a 6 week postpartum appointment. Participants will be asked to bring any remaining pills with them to that appointment at which time a research coordinator will collect the remaining pills, and record how many doses were missed. Any pills brought back by the patient will be given back to IDS to dispose of them. The research coordinator will also ask questions regarding any breastfeeding issues at this time. Furthermore, the charts of breastfed neonates will be followed to determine NICU admission or readmission during the first 6 weeks postpartum.

5.5 Study schedule

Procedure	At Enrollment	Within 1 day of delivery	Postpartum, in house	Postpartum, at home	Up to 10 days after discharge	Postpartum 6 weeks
Inclusion/exclusion and demographics	X	X				
Randomization	X	X				
Start intervention/ placebo		X				
Intervention/placebo			X	X		
Blood pressure collection	X		X	X	X	X
Maternal outcomes						X

5.6 Removal of Subjects from Study

Patients can be taken off the study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.4.1 Patient voluntarily withdraws from treatment (follow-up permitted);

5.4.2 Patient withdraws consent (termination of treatment and follow-up);

5.4.3 Patient is unable to comply with protocol requirements;

5.4.4 Patient experiences toxicity that makes continuation in the protocol unsafe;

5.4.5 Treating physician judges continuation on the study would not be in the patient's best interest;

5.4.6 Lost to follow-up.

If a research subject cannot be located to document outcomes after a period of 2 weeks, the subject may be considered "lost to follow-up." All attempts to contact the subject during the first 2 weeks after discharge will be documented and will not exceed more than 2 phone texting messages and 1 phone call with or without voicemails.

5.4.6 The study is stopped.

5.7 Protections Against Physical Risk

There is minimal risk to use of furosemide in the postpartum period. Furosemide is a commonly used drug in postpartum period and prior studies have not shown any adverse effects in this patient population. At the Hospital of University of Pennsylvania, furosemide has been used frequently as part of a postpartum hypertension protocol. A DSMB comprised of individuals who are not investigators on the trial will be utilized to monitor for adverse outcomes. A list of mandatory events that should be reported to the DSMB within 24 hours of occurrence will be supplied to all clinicians and research coordinators managing trial patients. The DSMB will stop the trial if there is a 20% increase in the rates of adverse outcomes (a composite outcome). The DSMB will review the data every 6 months. Also all serious adverse effect will be recorded and reported to the institutional review board.

5.8 Protection against Loss of Privacy/Breech of Confidentiality

In order to protect a potential subject's privacy, study staff will only approach potential subjects in a private setting. Once consented, we will take multiple steps to protect the study subject from breach of confidentiality. The list linking the subject's name and medical record number will be kept behind the hospital firewall in a password-protected file. This file is only accessible through the hospital server to those individuals given password approval to access the file. Furthermore, the electronic database (REDCap) will be coded with a unique study identifier rather than with any individually identifiable private information. No PHI will be shared with anyone outside the institution.

6 Response Criteria

6.1 Criteria for initiation of therapy

Therapy will be given after 6 hours from delivery.

Safety/tolerability

Analyses will be performed for all patients having received at least one dose of study drug.

7 ADVERSE EVENTS

7.1 Adverse Event Monitoring

Adverse event data collection and reporting will be done to ensure the safety of subjects who will enroll be enrolled in thus study. Adverse events will be reported in a routine manner at scheduled times during the trial. Additionally, certain adverse events will be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug/device, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2 Definitions

7.2.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

7.2.2 Severity of Adverse Events

The severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
Moderate (grade 2): the event causes discomfort that affects normal daily activities.
Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Life-threatening (grade 4): the patient was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

7.2.3.1 Results in death.
If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

7.2.3.2 Is life-threatening (i.e. the patient was at risk of death at the time of the event).

7.2.3.3 Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

7.2.3.4 Results in persistent or significant disability or incapacity.

7.2.3.5 Is an important medical event. Essentially, any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event.

For the purposes of this study, the adverse events that would meet any of these criteria are: maternal death, ICU admission, stroke, seizure, myocardial infarction, and cardiomyopathy will be documented and reported as a SAE. In addition, any unexpected event which the PI believes to have been cause or contributed to by the intervention, regardless of whether it resulted in hospitalization, will also be considered an AE or SAE (e.g., severe allergy or anaphylaxis due to furosemide).

7.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event

Step 2: Grade the adverse event

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

7.4 Reporting Requirements for Adverse Events

7.4.1 Expedited Reporting

- The Principal Investigator will be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- The University of Pennsylvania IRB must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR/UPIRSO).

  The following events meet the definition of UPR:

  1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
  2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
  3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
  4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
  5. Any breach in confidentiality that may involve risk to the subject or others.
  6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

7.4.2 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

7.5 Stopping Rules

This study does not have a primary safety endpoint or place study subjects at high risk. Please refer to section 11.2 for further discussion of Data Safety Monitoring.

8 DRUG/DEVICE INFORMATION

8.1 Furosemide

- Other names for the drug: Lasix
- Classification - type of agent: Loop diuretic; Antihypertensive
- Mode of action: inhibits reabsorption of sodium and chloride in the ascending loop of Henle and distal renal tubule, interfering with the chloride-binding co-transport system, thus causing increased excretion of water, sodium, chloride, magnesium, and calcium
- Protocol dose: 20 mg, daily
- Route of administration for this study: Oral
- Incompatibilities: NSAIDs may diminish the diuretic effect of loop diuretics. Loop diuretics may enhance the nephrotoxic effect of NSAIDs. Monitoring for evidence of kidney injury or decreased therapeutic effects of loop diuretics with concurrent use of an NSAID.
- Availability: commercially available, on formulary
- Side effects: ototoxicity, mood changes, confusion, muscle pain, palpitations, dizziness, syncope, increased thirst, fatigue, weakness, decreased appetite, dry mouth, dry eyes, upset stomach, nausea, and emesis associated with fluid and electrolyte problems (Please refer to the manufacturer's package insert for a complete list of adverse events)
- Nursing implications: PO administration should be on empty stomach

8.1.1 Product Preparation/Packaging, Receipt and Storage

Investigational Drug Service (IDS) of the University of Pennsylvania will purchase commercial furosemide 20mg tablets. These will be over-encapsulated into gelatin capsule shells and backfilled with Lactose Monohydrate, NF. The finished furosemide capsules will be placed in a light protected Type 2 HDPE plastic container with a tightly sealing lid. An internal lot number and use-by date will be assigned. The use-by date will be 12 month or the remaining expiration of any component (whichever is less). Visually-matching placebo capsules will be prepared by backfilling Lactose Monohydrate, NF into gelatin capsule shells. The finished placebo capsules will be placed in a light protected Type 2 HDPE plastic container with a tightly sealing lid. An internal lot number and use-by date will be assigned. The use-by date will be 12 month or the remaining expiration of any component (whichever is less).

IDS will dispense patient-specific study medication. IDS will package and deliver the drugs or study coordinators will pick them up as needed for participants. Drug accountability will be maintained by IDS and study coordinators.

Study medication (furosemide) will be stored at room temperature at IDS research pharmacy. Temperature is monitored in the investigational pharmacy daily. Once the

study medication or placebo are up on the floor, they will be stored at room temperature at a secure area for medications only accessible by floor and research staff.

9 STUDY DESIGN/STUDY ENDPOINTS

This will be a prospective, randomized, double-blinded, single center study of the impact of a short course of furosemide on postpartum blood pressure recovery in women with hypertensive disorders of pregnancy (HDP). Please refer to Section 2.4 for end points.

Regarding stopping rules for safety or efficacy, we do not anticipate early termination of the study for either. Issues that would be of concern would be persistent hypokalemia (< 3.0) with therapy, ineffectiveness of therapy (as defined by the use of the same dosing of other antihypertensive agents for blood pressure control), and unexpected events (admission to ICU). Other findings that could trigger a safety review include the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs, or increased frequency of events.

9.1 Sample Size and Accrual

The sample size is based on a current ongoing study at HUP in which 45.6% of patients had persistently elevated blood pressures 7 days after delivery. For a power of 80% and a statistical significance level of 5%, 175 patients would be needed to find a 40% reduction in blood pressures with the use of furosemide. In anticipation of possible post-randomization losses of approximately 10% of patients, we plan to recruit 385 participants for randomization in the two groups.

9.2 Data Analyses Plans

To account for the multiple measurements per patient, we will employ repeated measure regression techniques. Measures of relative risk will include 95% confidence intervals. Descriptive statistics will be presented as mean with standard deviation, median with interquartile range, or proportion with 95% confidence interval based on data type and distribution. Comparisons between groups will be performed using a Chi-square or Fisher's exact test for categorical variables and parametric or non-parametric tests for continuous variables, as appropriate. Bivariable analysis will be used to determine variables (risk factors) that are independently associated with PPHTN. Intention-to-treat analyses will be conducted such that all patients with available follow-up measures will be included in the analysis. Blood-pressure measurements after randomization will be compared between groups with the use of a mixed-effects logistic-regression model, which will account for participants having different numbers of observations over a varying time span. Statistical analyses were conducted in SAS, version 9.4 (SAS Institute, Cary, NC). Two-tailed P values of <0.05 will be considered statistically significant.

10 STUDY MANAGEMENT

10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the PI and the IRB. All investigators will follow the University's conflict of interest policy.

10.2 Collection of data

We will record data on each patient regarding their demographics, obstetrical and medical history, labor and delivery admission and any readmission information within 6 weeks postpartum.

10.2.1 Private information

Only the study staff listed on the protocol approved by the Institutional Review Board will have access to individually identifiable private information about human subjects. The only individually identifiable private information about human subjects that will be collected for research purposes is the subject's name and medical record number for the purpose of linking the subject to their unique study identifier.

10.2.2 Data Protection

The individually identifiable private information that will be collected is name and medical record number for the purposes on linking the subject to their unique study number for chart review. We will collect phone numbers as well in order to be able to text with patients in the postpartum period to collect their daily blood pressures. The file linking the study number to the name, medical record number and phone number will be kept in a password-protected file on a secure server. Data will be collected primarily by the research team. The electronic database (REDCap) will be stored behind the institution's firewall in a password-protected file.

10.3 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.4 Data Management and Monitoring/Auditing

10.4.1 Data Safety and Monitoring Plan

Safety monitoring will be performed periodically by the principal investigator. This will include assessment of accuracy of data recording, assuring de-identification of data, and that there is appropriate locked storage of data material. There will be no planned interim analyses. An advisory board will be created for continual oversight of the project. It will be comprised of faculty members within the department with extensive experience in prospective clinical trials. They will perform periodic reviews of safety data from this study. The DSMB that will be created is attached.

10.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.5.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, a IRB modification form must be completed within five (5) business days of making the change.

10.5.2 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, the ensuing guidelines will be followed:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Study personnel should report violations within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

10.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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