A randomized control trial of furosemide or placebo with usual antihypertensives in the antepartum management of severe hypertension with wide pulse pressure
Protocol Number I Version 2
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Section I: Purpose and Background

1. Purpose

Primary objective: To determine whether the addition of intravenous furosemide with usual antihypertensives is associated with a reduction in mean systolic blood pressure from baseline compared to treatment with placebo plus usual antihypertensives (intravenous labetalol, intravenous hydralazine, or oral immediate release nifedipine) for the management of severe antepartum hypertension.

Secondary objectives:
To determine whether the addition of intravenous furosemide with usual antihypertensives is associated with a reduction in mean diastolic blood pressure compared to treatment with placebo plus usual antihypertensives listed above.

2. Background

Introduce and provide support for the research being proposed. Basic information relevant to the context of the research question and study design should be included in this section. Additionally, this section should be written in a way that a person who is not an expert in the field can understand.

Blood pressure is a measure of blood flow and resistance in blood vessels. In normal pregnancy, total blood volume increases while systemic vascular resistance decreases, thereby leading to an overall reduction in blood pressure with return to baseline at term. Hypertensive disorders in pregnancy, including preeclampsia, are a polymorphic syndrome characterized by elevated blood pressures which can affect multiple organ systems[1]. Although the exact mechanism of preeclampsia has yet to be determined, previous studies have shown that there may be two distinct phenotypes – one characterized by vasoconstriction and diminished micro-circulation and the other involving a hyperdynamic high cardiac output state[2,3].

Given its potential for both significant maternal and fetal morbidity, hypertensive disorders in pregnancy comprise a substantial proportion of antepartum admissions. Management of acute severe hypertension (systolic BP$\geq$ 160 or diastolic BP$\geq$ 110) is important to reduce the risk of stroke, hypertensive encephalopathy, placental abruption, and heart failure or myocardial infarction[4]. In the antepartum and intrapartum period, the use of antihypertensives including labetalol, nifedipine, and hydralazine have been well-described[4]. Despite these options for blood pressure control, preeclampsia can be a progressive disorder that may not respond to the aforementioned agents.

In preeclampsia manifested by high blood volume due to salt and water retention rather than vasoconstriction, standard antihypertensives may be less effective. Furosemide is a commonly used diuretic that can lower blood pressure by inhibiting the absorption of sodium, chloride, and water, thereby decreasing the volume of blood that the heart pumps. The onset of action of action of IV furosemide is 5 minutes, with peak effect at 30 minutes, and duration of action of 2 hours[5].

Previous studies have demonstrated the safety and efficacy of furosemide to treat preeclampsia in the antepartum and postpartum period as well as its utility in treating heart failure in pregnant women[6,7]. To our knowledge, no randomized studies exist that investigate the use of furosemide in treating hypertension in the antepartum period. We aim to determine the utility of the addition of furosemide to usual antihypertensives in this clinical setting.

References

1. Grindheim G, Estensen ME, Langesaeter E, Rosseland LA, Toska K. Changes in blood pressure during healthy pregnancy: a longitudinal cohort study. J Hypertens. 2012 Feb;30(2):342-50. doi: 10.1097/HJH.0b013e32834f0b1c. PubMed PMID: 22179091.
2. Phillips JK, Janowiak M, Badger GJ, Bernstein IM. Evidence for distinct preterm and term phenotypes of preeclampsia. J Matern Fetal Neonatal Med. 2010 Jul;23(7):622-6. doi: 10.3109/14767050903258746. PubMed PMID: 20482241; PubMed Central PMCID: PMC2885458.
3. Easterling TR, Benedetti TJ, Schmucker BC, Millard SP. Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study. Obstet Gynecol. 1990 Dec;76(6):1061-9. PubMed PMID: 2234714.
4. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstet Gynecol. 2019 Jan;133(1):e1-e25. doi: 10.1097/AOG.0000000000003018. PubMed PMID: 30575675.
5. https://www.uptodate.com/contents/furosemide-drug information?search=furosemide&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1
6. Tamás P, Hantosi E, Farkas B, Ifi Z, Betlehem J, Bódis J. Preliminary study of the effects of furosemide on blood pressure during late-onset pre-eclampsia in patients with high cardiac output. Int J Gynaecol Obstet. 2017 Jan;136(1):87-90. doi: 10.1002/ijgo.12019. Epub 2016 Nov 3. PubMed PMID: 28099709.
7. Ascarelli MH, Johnson V, McCreary H, Cushman J, May WL, Martin JN Jr. Postpartum preeclampsia management with furosemide: a randomized clinical trial. Obstet Gynecol. 2005 Jan;105(1):29-33. doi: 10.1097/01.AOG.0000148270.53433.66. PubMed PMID: 15625138.
8. Duley L, Meher S, Jones L. Drugs for treatment of very high blood pressure during pregnancy. Cochrane Data- base of Systematic Reviews 2013, Issue 7. Art. No.: CD001449. (Systematic Review and Meta-Analysis). PMID: 23900968

9. Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period. Committee Opinion No. 692. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;129:e90–5. (Level III). PMID 28333820.

Section II: Criteria for Subject Selection

1. **Number of subjects**
   List the number of subjects expected to participate. For multi-center protocols include the overall projected total and site specific projected totals.

   This study expects to enroll 70 subjects and projects a retention rate of approximately 80%. Fifty-six subjects are expected to complete the study.

2. **Demographics of subjects**
   Describe the projected distribution of gender, age range, race and ethnicity of subjects. Support for the inclusion or exclusion of certain vulnerable populations (i.e. pregnant women, minors, minorities, age groups, etc.) should be included.

   This study expects to enroll pregnant females at least 18 years of age and at least 20 weeks of gestation with hypertensive disorder in pregnancy. No restrictions on race or ethnicity will be imposed. Since preeclampsia is a disease only encountered in pregnancy, and pregnant women are the only population to incur potential benefit from this body of evidence, it is vital that pregnant women be involved as subjects.

3. **Inclusion criteria**
   Define subject eligibility based on scientific rationale and safety considerations. Include the timeframe of data collection for retrospective studies.

   Inclusion Criteria

   - Subjects 18 years of age or older
   - Subjects with intrauterine pregnancy at or beyond 20 weeks of gestation
   - Subjects with a diagnosis of hypertensive disorder in pregnancy
   - Subjects with persistent (on repeat BP check 15 min apart) severe range blood pressure recordings (systolic BP≥ 160 or diastolic BP≥ 110) with wide pulse pressure (>60 mmHg)
   - Subject able to provide informed consent

4. **Exclusion criteria**
   Define exclusion criteria to limit the study population and prevent subjects from being exposed to excess risk by the study. Exclusion criteria should account for warnings, precautions, and contraindications listed in current product labeling.

   Exclusion Criteria
   - Subjects less than 18 years of age
   - Subjects with intrauterine pregnancy less than 20 weeks of gestation
   - Subjects with known fetal anomaly
   - Subjects with hypokalemia (K <3.0 mEq/L) on admission

- Subjects with anuria (<50mL urine in 24 hours) or renal failure
- Subjects previously taking diuretics or potassium supplements for any reason
- Subjects with a known allergy/adverse reaction to furosemide
- Subjects who are unable to understand and/or sign the informed consent
- Active labor (≥ 6cm dilated) or epidural in place

5. **Vulnerable subjects**
   Provide justification for the necessary inclusion of vulnerable populations. Vulnerable subjects often need additional protection and certain restrictions and requirements may apply. Children, pregnant women, and prisoner are examples of vulnerable populations.

   Preeclampsia exclusively affects pregnant individuals. As such, pregnant subjects should be studied. To protect these patients, consent forms will be collected and we will reiterate that declining study participation will in no way affect the quality of care they will receive.

Section III: Methods and Procedures

1. **Methods and procedures**
   Summarize the research design (observational, randomized, case-study, etc.) and include a schematic diagram if applicable. Provide a sequential list identifying all the procedures of the study, distinguishing between experimental procedures and procedures resulting from routine care. Explain procedures, situations, or materials that may be hazardous and subsequent precautions to reduce subject risk.

   This will be a prospective double-blinded randomized placebo control trial of women ≥20 weeks of gestation with persistent antepartum hypertension (sustained SBP ≥160 or DBP ≥110 mmHg) and a wide pulse pressure (>60 mmHg) who meet all inclusion criteria and have no exclusion criteria. It is routine that laboratory studies are performed on admission for all women with hypertensive disorders. If electrolyte disturbances exist, therapy will not be initiated unless the electrolyte is normalized or repleted.

   After informed consent and upon meeting inclusion criteria with severe range hypertension with wide pulse pressure, the study personnel will inform pharmacy personnel who will then randomly assigned the patient to groups by opening the next previously prepared sequential and numbered opaque study envelope. Participants will be randomized to furosemide plus an antihypertensive versus placebo containing normal saline and an antihypertensive. The pharmacy staff will send the assigned treatment, which will be administered by the bedside nurse. The vials containing the treatment will be indistinguishable as both furosemide and normal saline placebo are clear, colorless solutions. Thus, the provider, nurse, and patient will be blinded to the treatment. The choice of antihypertensive will be determined by the primary OB provider. At our institution, this will be one or more of the recommended medications for urgent blood pressure control as outlined by the American College of Obstetricians and Gynecologists Practice Bulletin on gestational hypertension and preeclampsia. These include IV labetalol, IV hydralazine, or immediate-release oral nifedipine. As meta-analyses have not shown that one of the aforementioned antihypertensives is superior than another, and all are reasonable options, the choice of antihypertensive will be left up to the OB

provider[8,9]. This will also improve the generalizability of the study as it does not interfere with what is typically done in clinical practice.

As a procedure of the study, patients will have their blood pressure recorded at least every 15 minutes up to one hour after administration of the study drug. Thereafter, as part of routine care, patients in both groups will receive similar antepartum surveillance, including blood pressure and pulse assessment every four hours or more frequently if vital signs are abnormal, daily weight measurement, and daily urinary output measurements.

Study Procedures

1. Antepartum patient diagnosed with a hypertensive disorder in pregnancy.
2. Patient approached for study participation and informed consent obtained if interested.
3. Patient develops severe range BP (SBP>160 and/or DBP>110) with increased pulse pressure (>60mmHg). This will be considered baseline BP.
4. When ordering provider's choice of antihypertensive, pharmacy notified that patient is study participant and randomizes patient by choosing from sequential opaque envelope.
5. a. Patient randomized to treatment arm and receives 40mg /4mL IV furosemide in addition to usual antihypertensive.
   b. Patient randomized to placebo and receives 4mL normal saline in addition to usual antihypertensive.
6. Blood pressure check every 15 minutes after administration of furosemide/placebo for four recordings (15, 30, 45, 60 minutes)

2. **Data analysis**
   Specify statistical and analytical methods (statistical power, sample size, significance level, etc.).

The primary outcome variable is reduction in mean systolic BP during the 1-hour period after drug administration. BP will be taken every 15 minutes for 1 hour and averaged. Intention-to-treat analysis will be performed. This study will use a two-sided t-test with the null hypothesis set at the standard significance level (p –value < 0.05), to determine if the addition of furosemide to usual antihypertensive significantly reduces blood pressure.

Change in average BP from baseline will be tested comparing the group receiving furosemide and the group receiving placebo using Mann-Whitney U, as BP usually presents as a non-parametric continuous variable. Multivariate regression will be used to adjust for potential confounders, such as maternal age, BMI, diabetes, baseline BP, antihypertensive chosen by the primary obstetrician, number of doses of antihypertensive, and gestational age. Comparative testing will be done to explore differences between the furosemide and placebo groups. Continuous variables satisfying the assumption of normality will be tested using the Student t-test and means and standard deviations will be reported. Otherwise, variables will be tested using the Mann-Whitney U test and will be reported using medians and interquartile ranges. The $\chi 2$ or

Fisher exact test will be utilized to test categorical variables and sample sizes and percentages will be reported.

A power calculation was completed using OpenEpi, Version 3, open source calculator—SSMean. The assumption of normality and that both groups will have the same common variance was applied. We set the standard deviation value as 20mmHg in the power calculation, which is based on pilot data from our own practice as well as data found in a randomized clinical trial using furosemide versus placebo (Ascarelli et al, Ob/Gyn 2005). A 15mmHg reduction in mean systolic blood pressure in the placebo group compared with the IV furosemide group was considered to be clinically significant as this represents an attainable, yet safe reduction from severe to mild range blood pressure. Using the 2-group Student t-test of equal means, 28 patients per study arm for a total of 56 patients would be required to detect a difference of 15mmHg with 80% power and a significance level of p=0.05. Once data has been collected, we will test for normality and use the appropriate statistical tests.

To account for patients who withdraw from the study or who need to be excluded after consent, 35 per arm or 70 total patients are to be enrolled. A randomization schedule will be created using block randomization with 10 blocks of 10 participants allocating randomization numbers to drug or placebo. The numbers will be sequentially assigned to participants by the pharmacist on duty. The hospital pharmacy will maintain the master list of the randomization log with patient study identifiers.

Data monitoring
Describe data monitoring methods for studies with more than minimal risk (i.e. data monitoring committee). Explain adverse event reporting procedures.

This is a greater than minimal risk study. Adverse events will be reported to the sub-investigator and primary investigator by the nurse and/or the obstetric provider. Furthermore, the sub-investigator will be actively following study participants closely to monitor for adverse events. If found, these will be reported to the institutional review board according to their reporting polices.

3. **Data storage, security, and confidentiality**
Describe where data will be stored and how data will be secured during the study. Provide information on confidentiality measures (coding, storage mechanisms, etc.). Indicate who will have access to the data and how the data will be used. If subject identifiers will be released, describe to whom and for what purpose the data will be released.

Data will be stored on a password-protected computer and maintained for 10 years after study completion. The data will be recorded in Microsoft Excel and will only be transmitted electronically through UCERA's encrypted email service among other study personnel in the same encrypted network. Access to subject data will be limited to the principal investigator, sub-investigators, and study staff. Data will be de-identified when data collection is complete, at which time each subject will be given a subject ID number. A key containing subject ID numbers will be maintained by the investigator and sub-investigator. Data will only be used for research purposes.

4. **Data Sharing**
   Describe plans for data sharing, particularly for publication purposes. Many journals now require authors to disclose how de-identified individual level data will be shared. Some journals require data sharing plans to be posted in a public registry, such as Clinicaltrials.gov. Additional information about data sharing can be found here:
   https://grants.nih.gov/grants/sharing_key_elements_data_sharing_plan.pdf
   https://grants.nih.gov/grants/policy/data_sharing/data_sharing_workbook.pdf

   The following statements are in response to data sharing guidelines by Elsevier.

   Will individual participant data be available (including data dictionaries)?
   Individual participant data will be made available.

   What data in particular will be shared?
   Individual participant data that underlie the results reported any future manuscript, after deidentification (text, tables, figures, and appendices).

   What other documents will be available?
   There are no plans for additional documents to be made available.

   When will data be available (start and end dates)?
   Beginning 9 months and ending 36 months following any publication.

   With whom?
   Researchers who provide a methodologically sound proposal.

   For what types of analyses?
   To achieve aims in the approved proposal.

   By what mechanism will data be made available?
   The data will be deposited to Mendeley Data, a data repository that is supported by Elsevier and the American Journal of Obstetrics & Gynecology.

5. **Transition from research participation (if applicable)**
   Describe how subjects who terminate participation will be transitioned to regular care (such as, taper study medication, return to primary care provider).

   Subjects who terminate participation will resume regular care as determined by her primary treatment team. The investigators will discontinue collecting data on the individual and the choice of medications for acute blood pressure control will no longer be influenced by the investigators or study protocol.

Section IV: Risk/Benefit Assessment

1. **Risk category (Contact HPHRI if you need assistance determining risk level)**
   State the risk of participating in the study as either Minimal or Greater than Minimal. Risk is defined as the potential harm associated with the research that a

reasonable person would find injurious. Minimal Risk means that the probability or magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Participation in this study presents greater than minimal risk to subjects but not greater than the risks incurred by their existing disease process. As patients admitted with severe preeclampsia are required to have intravenous access, no additional invasive lines would be placed for the sole purpose of administering the study medications. Additionally, furosemide is already used for the aforementioned indication (severe range blood pressure with wide pulse pressure) in pregnant women. As furosemide is an approved drug being used for its approved indication in this study (ACC/AHA [Whelton 2017], risks incurred to the patient are outweighed by the potential benefit of treating a life-threatening condition (severe range blood pressure).

2. **Potential risk(s)**
Describe any potential risks associated with the study (physical, psychological, sociological, economic, and/or legal). If possible, estimate the probability of a given risk and potential reversibility.

Potential risks associated with participation in this study include the known pharmacologic effect of furosemide, which include fluid/electrolyte loss as well as rare side effects such as.

Cardiovascular: Necrotizing angiitis, orthostatic hypotension, thrombophlebitis, vasculitis
Central nervous system: Dizziness, headache, paresthesia, restlessness, vertigo
Dermatologic: Acute generalized exanthematous pustulosis, bullous pemphigoid, erythema multiforme, exfoliative dermatitis, pruritus, skin photosensitivity, skin rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria
Endocrine & metabolic: Glycosuria, hyperglycemia, hyperuricemia, increased serum cholesterol, increased serum triglycerides
Gastrointestinal: Abdominal cramps, anorexia, constipation, diarrhea, gastric irritation, mouth irritation, nausea, pancreatitis, vomiting
Genitourinary: Bladder spasm
Hematologic & oncologic: Agranulocytosis, anemia, aplastic anemia, eosinophilia, hemolytic anemia, leukopenia, purpura, thrombocytopenia
Hepatic: Hepatic encephalopathy, intrahepatic cholestatic jaundice, liver enzymes increased
Hypersensitivity: Anaphylaxis, anaphylactoid reaction, anaphylactic shock
Immunologic: DRESS syndrome
Neuromuscular & skeletal: Muscle spasm, weakness
Ophthalmic: Blurred vision, xanthopsia
Otic: Deafness, tinnitus
Renal: Interstitial nephritis (allergic), renal disease
Miscellaneous: Fever

Source: https://www.uptodate.com/contents/furosemide-drug information?search=furosemide&source=panel_search_result&selectedTitle=1~148&usage_type=panel&kp_tab=drug_general&display_rank=1

3. **Protection against risk(s)**
   Describe how the study will minimize or prevent any potential risks. Techniques to minimize risk include subject monitoring, withdrawal criteria, and follow-up procedures.

   Subjects will be monitored for side effects and dosage levels will be adjusted if the subject experiences side effects from furosemide. Subjects will not receive additional furosemide if side effects are deemed significant. Subjects will be allowed to withdraw from the study at any time without consequence. If new information about the study becomes available, subjects will be informed and re-consented if applicable.

4. **Potential benefit(s) to the subject**
   Describe any potential medical benefit(s) for subject participation. State if participation results in no benefit to the subject.

   The direct medical benefits to the subject for participating in the study include acute control of severe hypertension, which reduces the risk of stroke, placental abruption, hypertensive encephalopathy, and myocardial infarction. An additional benefit may include prolongation of pregnancy at critical gestational ages which may reduce the risks of prematurity which includes respiratory distress, intraventricular hemorrhage, necrotizing enterocolitis, and metabolic and thermic dysregulation.

5. **Alternative to participation**
   Describe any alternative therapies or courses of action available to the subject if they decide not to participate in the study.

   Should a subject decide not to participate in the study, they will receive the standard of care for severe hypertension, which typically includes IV labetalol, IV hydralazine, or oral immediate-release nifedipine. However, furosemide is an adjunct that may be administered to the patient per the primary clinician's decision, unrelated to the study.

Section V: Subject Identification, Recruitment and Consent/Assent
(If you are requesting a waiver of consent this section can be deleted)

1. **Method of subject identification and recruitment**
   Describe how subjects will be identified and recruited. Include steps to minimize undue influence if recruitment includes an investigator's students, employees, and/or patients.

   Contact will be initiated in person at the time of severe range blood pressure and meeting inclusion criteria by the antepartum care provider. If eligible, individuals who are involved in the study and identified as key study personnel will provide information about the study to the subject and if the subject is interested will proceed with obtaining informed consent. Subjects will be informed of the voluntary nature of the study and informed of alternative treatment options.

2. **Consent process**

List study team members authorized to obtain consent and describe the process of informed consent.

Informed consent will be primarily conducted by the sub-investigators, principal investigator, and trained residents and fellows who have completed the necessary training for research clearance. The subject will be approached with study information as close to the time at which she meets inclusion criteria, which in many cases will be at the time of admission. If the study participant is not ready to make a decision regarding their participation at the time of informed consent, then the study personnel will return later that day or the next. The informed consent process will consist of reviewing the informed consent documents and asking the subject a series of questions to ensure comprehension (see subject/representative comprehension below).

3. **Subject capacity (if applicable)**
   Describe how capacity will be assessed and by whom. State the anticipated degree of impairment relative to the subject's ability to consent.

   Capacity will be assessed by the admitting provider at the time of the admission history and physical by directed clinical interview and exam. This includes the ability to understand information about treatment; the ability to appreciate how that information applies to their situation; the ability to reason with that information; and the ability to make a choice and express it. We anticipate there to be no degree of impairment relative to the subject's ability to consent.

4. **Subject/Representative comprehension**
   Describe how it will be determined that the subject /representative understood the information presented during the informed consent process. If children or decisionally impaired adults will participate, include a plan to assess comprehension during the assent process.

   To determine comprehension of the informed consent, subjects will be asked a series of questions. These include:

   1. Can you briefly recount the purpose of the study and your involvement?
   2. What is your understanding of your decision to participate in the study, to decline participation, or to discontinue participation after being initially involvement and how this impacts the care you receive?
   3. In case you have further questions about the study or your involvement, are you aware that you may contact the investigators?

5. **Documentation of consent**
   If not addressed in the process of consent section, explain how consent will be documented and where documentation will be stored.

   Consent will be documented on the Hawai'i Pacific Health Research Institute IRB-approved informed consent form and by the subinvestigator's password-protected electronic log. Paper documentation will be stored by the subinvestigator in a locked-file

cabinet and electronic documentation will be stored on a password-protected computer. A copy of the signed consent form will be provided to the subject and will be scanned into the electronic medical record.

6. **Costs to the subject**
   There will be no costs incurred by the subject as a result of participating in the study as this is part of global inpatient pregnancy care and the medications in this study are commonly used in the inpatient setting for the aforementioned medical indications.

7. **Payment for participation**
   There will be no payment for participation in this study.