Treatment of Persistent Non-Severe Postpartum Hypertension

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Purpose of the Study

Objective 1: Compare the average blood pressure of women with non-severe hypertensive disorders of pregnancy with and without treatment with nifedipine extended release at 1 week and 4 weeks postpartum.

We hypothesize that treatment with nifedipine extended release compared with no treatment will significantly reduce the average blood pressure at 1 week and 4 weeks postpartum in women with non-severe hypertensive disorders of pregnancy.

Objective 2: Determine the proportion of women with non-severe hypertensive disorders of pregnancy whose postpartum blood pressure at 1 week and at 4 weeks are normotensive (<130/80 mm Hg) per new American College of Cardiology and American Heart Association (ACC/AHA) guidelines with and without treatment with nifedipine extended release.

We hypothesize the proportion of women with non-severe hypertensive disorders of pregnancy who are normotensive per ACC/AHA guidelines at 1 week and 4 weeks postpartum will be higher among the women treated with nifedipine extended release compared women without treatment.

Background & Significance

BACKGROUND

a) Prevalence of postpartum hypertension

Hypertensive disorders of pregnancy include chronic hypertension, gestational hypertension, and preeclampsia. Chronic hypertension affects 1.5% of pregnancies; gestational hypertension and preeclampsia affect ~4-8% of pregnancies. The rate of hypertensive disorders of pregnancy is rising, in part, due increasing obesity and delayed childbearing leading to increased maternal age during pregnancy. Postpartum hypertension, which may be a new diagnosis or a continuation of a hypertensive disorder of pregnancy, affects ~2% of recently pregnant women. Of that 2%, gestational hypertension and preeclampsia make up 86% of postpartum hypertension cases.

b) Current treatment recommendations for postpartum hypertension

Severe range blood pressure ≥160/110 mm Hg should be treated promptly in the postpartum period to reduce the risk of stroke. Acute severe postpartum blood pressure elevations are generally treated with one of three agents: intravenous labetalol, intravenous hydralazine, or oral immediate-release nifedipine. All three medications are considered safe and effective for management of severe postpartum hypertension and are considered 1st line therapy.

The treatment of persistently elevated non-severe blood pressure in the postpartum period is the interest of this proposal. In its newest hypertension in pregnancy guidelines, ACOG does not provide any specific guidelines for management of postpartum hypertension. The two most commonly used long-

acting oral anti-hypertensive used for postpartum hypertension are labetalol and extended-release nifedipine.

SIGNIFICANCE

a) Postpartum hypertension is a significant contributor to severe maternal morbidity and maternal mortality

In the United States, there has been a recent focus on improving maternal mortality and severe morbidity. The maternal mortality rate in the United States has increased from 9.9 per 100,000 births in 1999 to 26.4 per 100,000 births in 2015, making it one of the highest maternal mortality rates among industrialized nations. This increase is most notable among non-Hispanic black women who had a mortality rate of 46 per 100,000 births in 2014. More common, however, is severe maternal morbidity (SMM), which increases the risk for maternal mortality. SMM can be explained as adverse outcomes of the process of labor and delivery that result in significant short-term or long-term consequences to a woman's health. The Center for Disease Control and Prevention defines SMM by 18 indicators commonly identified as peripartum complications. Severe maternal morbidity, like maternal mortality, has also significantly increased over the last 2 decades, from 49.5 per 10,000 births in 1993 to 144.0 per 10,000 births in 2014.

Hypertensive disorders of pregnancy such as preeclampsia and gestational hypertension are strongly associated with SMM including stroke, eclampsia, renal failure, and cardiomyopathy. Studies have shown that women with SMM are significantly more likely to have been diagnosed with a hypertensive disorder of pregnancy .

b) ACOG does not provide robust guidance on the management of BP in the postpartum period

There is very limited data on which antihypertensive agent provides the best control of blood pressure in the postpartum period. One small randomized controlled trial (n=50) compared oral labetalol and nifedipine extended release for persistent postpartum hypertension in women with no previous therapy (17). The primary outcome was time to blood pressure control, which was not different between the two groups. Interestingly, blood pressure information was only available in 48% of women at 72 hours, 20% women at 1-2 weeks, and 16% of women at 4-6 weeks.

Outside of recommending treatment for postpartum blood pressure that is persistently above 150/100 mm Hg and using labetalol or nifedipine extended release, ACOG does not provide explicit guidance on initial dose of therapy, dose adjustments, duration of therapy, or parameters for discontinuing antihypertensive therapy. Additionally, many women who have gestational hypertension or preeclampsia, will have normalization of blood pressure without medical intervention. There is no data to evaluate spontaneous normalization of blood pressure as compared to women who are prescribed anti-hypertensive therapy for postpartum non-severe postpartum hypertension.

c) ACC/AHA most recent blood pressure guidelines recommend blood pressure goal of <130/80 mm Hg in non-pregnant adults. No data on if women with hypertensive disorders of pregnancy are meeting this goal at their postpartum visit.

In 2017, the American College of Cardiology and American Heart Association Task Force on Clinical Practice Guidelines released new guidance for the diagnosis and treatment of hypertension which replaced the Joint National Committee 8 recommendations (JNC8) (18). Of note, hypertension was

classified into 4 stages, and normotensive blood pressure was defined as blood pressure < 130/80 mm Hg. Additionally, the use of blood pressure lowering medication is recommended for primary prevention of cardiovascular disease in adults with no history of cardiovascular disease when blood pressures are >140/90 mm Hg. If adults have a ≥10% risk of 10-year atherosclerotic cardiovascular disease (ACVD) or history of cardiovascular disease, blood pressure lower agents should be initiated if blood pressure ≥130/80 mm Hg. The 10-year ACVD risk will be unknown for most postpartum patients. However, many of our patients will have common risk factors for CVD. Pregestational diabetes affects 3-7% of pregnancies (19). Approximately 32% of reproductive age women ages 20-39 are obese (20). Increasing maternal age should also be a consideration for management of postpartum hypertension, given that older women are increased risk of adverse outcomes postpartum (21). Taken together, more research is needed to optimize treatment of postpartum hypertension especially in light of recent change management of non-pregnant adults.

Design & Procedures

This study is a pilot, open-label randomized controlled trial of postpartum women with hypertensive disorder pregnancy and non-severe, but elevated postpartum blood pressure. Potential study patients will be approached by a member of the study team during the postpartum period of the patient's delivery admission.
Exposures groups will be treated with nifedipine extended release and no treatment for non-severe postpartum hypertension. Patient will be randomized 1:1 fashion. The primary outcome of this study is average systolic blood pressure at 1 week postpartum. Blood pressure will be obtained at a 1-week blood pressure check. Alternatively, women will also be provided blood pressure cuffs and be able to check their blood at home at 1 week and submit result via text. Secondary outcomes will include average diastolic blood pressure at 1 week postpartum, average systolic and diastolic blood pressure at 4 weeks postpartum, percentage of patient with blood pressure < 130/80 mm Hg at 1 week and 4 weeks postpartum, method of feeding, ED/triage visits, increase in blood pressure medication at 1 week postpartum visit, initiation of blood pressure medication at 1 week postpartum visit for patients in the no treatment group, addition of 2nd blood pressure medication at 1 week postpartum visit, and hospital readmission.

Once informed consent has been obtained and the patient is deemed eligible for participation, patients will be randomized prior to discharge from Duke Birthing Center of Duke University Hospital. Subjects randomized to the treatment group will be provided the study drug (nifedipine extended release) at an initial dose of 30mg daily in 1-month supply. The control group will not receive any drug for blood pressure control, which is standard practice for patients with non-severe postpartum hypertension.

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Dose adjustment of the treatment drug will be at the discretion of the obstetric provider, but a treatment algorithm will be provided for guidance. The use of an additional beta blocker (eg Labetalol) can be used at the discretion of the obstetric provider. This additional beta blocker is NOT a study drug

being investigated. Subjects in the no treatment group should not be started on medication at the 1-week postpartum visit unless blood pressure exceeds 160/110 mm Hg.

Subjects in both groups will be scheduled in the for a 1-week postpartum blood pressure check and routine 4 week postpartum visit in the Duke Perinatal Clinic as is standard of care at Duke for all patient with hypertensive disorders of pregnancy. Medication compliance in the treatment group will be assessed via validated questionnaire. As this is a pragmatic, pilot trial our control group is the current standard care for patients with persistent, non-severe postpartum hypertension instead of placebo.

Selection of Subjects

Inclusion criteria

- Antepartum diagnosis of gestational hypertension
- preeclampsia
- superimposed preeclampsia without antepartum chronic hypertension medication
- Delivery at 23 weeks or greater
- Persistent elevation in BP >12 hours postpartum (>/= 140/90 mm Hg) (2 or more documented BP)
- 18 years or older
- English speaking

Exclusion criteria

- Need for continuation of antepartum antihypertensive medication
- Contraindication of calcium channel blocker use
- Severe range (160/110 mm Hg) blood pressure requiring treatment >24 hours after delivery
- Requires a 2nd oral antihypertensive medication for blood pressure control inpatient
- Acute cardiomyopathy or heart failure
- Creatinine ≥1.5
- Blood pressure <90/60 within 24 hours of discharge

Study Interventions

The treatment group will provided with month supply of 30mg tablets of nifedipine extended release prior to discharge from the delivery admission. Dose increases in clinic will be at the discretion of providers, however a treatment algorithm will be provided for guidance.
The control group will not receive any medications at discharge. Providers will be instructed to only prescribe new blood pressure medication at subsequent postpartum visits if the blood pressure is in the sever range (>/=160/110).
Both groups will be given a home blood pressure cuff prior to discharge with instructions for use. They will also be scheduled for a 1 week blood pressure check and 4 week postpartum clinic appointment which standard for these patients outside of this proposal.

Risk/Benefit Assessment

Risks for this study are minimal. Patients will provide information regarding blood pressures that should prompt contacting medical personnel. Side effects will also be assessed each postpartum visit. Nifedipine extended release may cause some, all or none of the side-effects listed below.

More likely

- Flushing
- Headache
- Dizziness
- Nausea
- Peripheral swelling

Less Likely

- Low blood pressure
- Muscle cramps
- Shortness of breath, wheezing
- Mood swings, nervousness
- Palpitations
- Itching
- Constipation
- Chest pain
- Special Considerations
- Nifedipine extended release is safe for women who are breastfeeding.

There is also a small risk of loss of confidentiality.

Participants in this study will be provided a home blood pressure cuff to check blood pressures at home which may provide more expedited medical attention for severely elevated blood pressures. Women with hypertensive disorders of pregnancy are at increased risk of developing hypertension later in life. All participants will be referred to primary care physician in order facilitate blood monitoring and health maintenance care outside of pregnancy.

Data Analysis & Statistical Considerations

Sample size calculation

Based on an expected average systolic postpartum blood pressure of 140 mmHg at randomization and standard deviation of 15 points, a sample size of 40 per group is needed to detect a 10 point change in systolic blood pressure with at least 80% power and alpha of 0.05. Assuming a study attrition rate of 20%, an additional 10 subjects per study group will be enrolled. The total goal enrollment is 100 participants (50 in each group) If subject recruitment is lower than expected, we calculated an alternative power calculation. Based on an expected average systolic postpartum blood pressure of 140mmHg at randomization and standard deviation of 15 points, a sample size of 21 per group is needed to detect a 15 point change in systolic blood pressure with 90% power and alpha of 0.05.

Assuming a study attrition of rate of 20%, an additional 4 subjects per study group will be enrolled. The total enrollment using this alternative power calculation 50 (25 in each group).

Statistical analysis plan

Baseline characteristics (demographics, comorbidities, and obstetric history) will be summarized with mean (standard deviation) or n (%) by treatment and control groups. The primary outcome will be presented and compared between two groups using a two-sample t-tests with equal variance. Normality assumption on empirical distribution of the primary outcome will be evaluated. If this assumption is violated, non-parametric Wilcoxon rank rum test will be used. Secondary outcomes will also be summarized and compared between groups using two-sample t-tests with equal variance for continuous outcomes or Chi-square tests for categorical outcomes. A planned, exploratory subgroup analysis will be performed to compare the treatment effect in participants with and without antepartum diagnosis of preeclampsia with severe features. Two-sided tests at $P<0.05$ will be considered statistically significant. All analyses will be performed in SAS 9.4 (SAS Institute Inc., Cary, NC). Statistical support will be provided by Tracy Truong, MS and Alaattin Erkanli, PhD.

Data & Safety Monitoring

Subjects in both study groups will be provided with home blood pressure cuffs at discharge. They will instructed to check blood pressure daily for 1 week postpartum and weekly thereafter. Subjects will instructed to contact on-call OB providers if they have home blood pressure < 90/60 or >/=160/110. The contact for the OB triage, OB provider on call will be provided to patients. Subjects will be assessed for potential symptoms of nifedipine extended release at 1 week and 4 weeks postpartum visits. Patients will referred to or given information for a primary care physician to for continued follow-up outside of the postpartum period.

A Data Monitoring Committee (DMC) will be created to perform regular and timely review of data semi-annually in order to identify early, significant benefit or harm for patients while the trial is in progress. Non-identified safety data will be communicated to the DMC who will then meet to review the data. The DMC will be composed of three faculty members within the Duke University Department of Gynecology and Obstetrics. Individuals who are investigators or co-investigators cannot be members. Members must have no financial, scientific, or other conflicts of interest with the study. All investigators understand that the DMC serves as additional human subject's protection, but does not supplant reporting of significant adverse events to the Duke IRB. The DMC may devise its own stopping rules, and if there are significant numbers of adverse events, the DMC will recommend continuation, modification, or termination of the study after each meeting. This recommendation will be communicated to the Principle investigator who is responsible for reviewing the recommendation and forwarding it to the IRB. All investigators understand that the DMC may recommend their own "stopping rule" if other events occur which indicate a significant risk to study subjects.