PROTOCOL TITLE: Amlodipine versus nifedipine ER for the management of postpartum hypertension: A randomized controlled noninferiority trial

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PROTOCOL SYNOPSIS

Study Title	Amlodipine versus nifedipine ER for the management of postpartum hypertension: A randomized controlled noninferiority trial
Funder	Prisma Health OBGYN Departmental Research Fund
Study Rationale	-A significant number of pregnancies are complicated by hypertensive disorders (chronic hypertension, gestational hypertension, preeclampsia) -Hypertension is often exacerbated in the postpartum period -Many of these patients require initiation of antihypertensives after delivery -There are a limited number of well-studied treatment options routinely used (labetalol and nifedipine ER) -Prior studies have shown that both labetalol and nifedipine ER are effective -Nifedipine ER has few contraindications, but has significantly more side effects than labetalol -Headache is one of the most commonly reported side effects with nifedipine ER -Headache is also a commonly reported symptom of preeclampsia -Amlodipine is in the same drug class as nifedipine ER, but does not cause headaches -Amlodipine is a first-line antihypertensive in the non-obstetric population -Amlodipine has not been studied in the obstetric population
Study Objectives	Primary -To evaluate whether amlodipine is noninferior to nifedipine ER in the management of postpartum hypertension Secondary -To evaluate whether patients tolerate amlodipine better than nifedipine ER
Study Design	Unmasked, pragmatic randomized controlled trial

Subject Population	Inclusion criteria -English and Spanish-speaking postpartum women with a diagnosis of chronic hypertension, gestational hypertension, or preeclampsia -Delivery at or beyond 20 weeks' gestation -Need for antihypertensive therapy, defined as blood pressure >/= 150 mmHg systolic and/or 100 mmHg diastolic on two occasions four hours apart, or one severe blood pressure >160 mmHg systolic and/or 110 mmHg diastolic. -Age 18 years or older Exclusion criteria -Use of antihypertensives prior to delivery (either for hypertension or other indications, i.e. tachycardia) -Allergy to nifedipine ER or amlodipine -Persistent tachycardia (as defined by the treatment team)
Number of Subjects	160
Study Duration	Each subject's participation is expected to last less than 8 weeks The entire study is expected to last 24 months
Study phases	-Screening: Women admitted to Greenville Memorial Hospital Family Birthplace will be screened on admission to determine if they have a hypertension diagnosis. Additionally, postpartum women on the Women's Specialty unit who do not meet criteria prior to delivery will be rescreened once daily. Women with hypertensive diagnoses will be approached about their willingness to participate in the study, either at the time of admission or at time of diagnosis. -Randomization: Participants will be randomized to either nifedipine ER or amlodipine at the time of enrollment. In order to maximize participant capture, all screened patients who have a hypertensive diagnosis and agree to study participation will be consented and randomized. Only those who progress to needing antihypertensives will meet full inclusion criteria and ultimately be enrolled in the study. -Intervention: Those participants meeting inclusion criteria for antihypertensives will be administered the study medication. Participants will be administered either amlodipine or nifedipine ER, depending on their treatment arm allocation.

	-Follow-up: Data regarding the patient's need for additional medications, side effects, and length of stay will be collected throughout the hospitalization. Patients will attend a blood pressure check visit ideally 3 to 7 days after hospital discharge (virtual (for patients with home blood pressure cuff only) or in-person) and a postpartum visit ideally 4-6 weeks after delivery (in person), per standard of care. Additional data will be collected at these visits.
Safety Evaluations	While hospitalized, patients will be monitored daily by the clinical team to assess for side effects and ensure adequate blood pressure control. Adjustments will be made by the clinical team as indicated based on patient status. After hospital discharge, patients will be able to call the office with any concerns and additional appointments for evaluation can be made as necessary.
Statistical and Analytic Plan	Noninferiority of amlodipine will be assessed with Wilcoxon Rank-Sum
Data and Safety Monitoring Plan	Participants will be provided with contact information for the PI should they have any concerns.

1 BACKGROUND AND RATIONALE

Hypertensive disorders of pregnancy are a major cause of maternal morbidity and mortality, and it is felt that at least a portion of these adverse outcomes are preventable[1]. Worldwide, between 2 and 8 percent of pregnancies are complicated by preeclampsia[2]. Additionally, 0.9 to 1.5 percent of pregnant women have pre-existing chronic hypertension[3]. Postpartum hypertension can either be due to an exacerbation of existing chronic hypertension or preeclampsia, or it can be new onset[2,4]. Blood pressures tend to increase in the postpartum period, peaking at three to six days postpartum. It is not uncommon for women who did not require medications during the pregnancy to be started on an antihypertensive in the postpartum period[3,5]. If blood pressures are greater than or equal to 150 mmHg systolic and/or 100 mmHg diastolic on two occasions four to six hours apart, antihypertensive therapy is recommended[4,6,7].

The most commonly used antihypertensive medications in the postpartum period are labetalol and nifedipine ER. Studies have shown that nifedipine ER is at least as effective, and potentially even more effective, than labetalol in achieving blood pressure control[4,7]. However, significantly more patients have side effects when taking nifedipine ER (48% versus 20%), and 24% of women using nifedipine ER report headache as a side effect[7]. Headache is a known symptom of preeclampsia, and its presence as a symptom can change patient management. When patients are using nifedipine ER, it can be difficult to determine if the headache is due to the medication or the disease, making management decisions difficult.

Like nifedipine ER, amlodipine is a dihydropyridine calcium channel blocker[8]. Headache is not a commonly reported side effect of amlodipine. Amlodipine is not commonly used in the postpartum setting, but a prior study in the non-obstetrical population demonstrated that amlodipine and nifedipine ER resulted in comparable reductions in blood pressure and can be considered equivalent. Amlodipine was also found to have a significantly lower rate of side effects than nifedipine ER (27% versus 41%)[9].

Nifedipine ER is considered safe in breastfeeding women. Typically, a relative infant dose (RID) less than 10% is considered safe, and nifedipine ER has a RID of 2.3%. There is limited data on amlodipine use in breastfeeding women, and therefore the LactMed Database currently recommends an alternative to amlodipine if possible. However, one study has shown that the median RID for amlodipine is 4.18%, suggesting it is safe to use in breastfeeding women. In addition, multiple case reports of breastfeeding mothers using amlodipine did not demonstrate any adverse effects in the infant[10]. Although further data should continue to be collected, these prior studies and case reports are reassuring.

We hypothesize that amlodipine will be as effective as nifedipine ER in controlling blood pressures in patients with postpartum hypertension, as reflected by equivalent times from delivery to hospital discharge. In addition, we hypothesize that women taking amlodipine will report fewer side effects than those taking nifedipine ER. No effects on breastfeeding outcomes are expected.

1.1 Description of Intervention

Amlodipine and nifedipine ER are both dihydropyridine calcium channel blockers. In women with hypertensive disorders who meet criteria for initiation of treatment as outlined above, the allocated treatment will be initiated by the inpatient clinical team. The recommended starting dose for nifedipine ER will be 30 mg daily and the recommended starting dose for amlodipine will be 2.5 mg daily. Doses will be adjusted as needed by the clinical team. Patients will be treated with additional short-acting antihypertensives, additional long-acting antihypertensives or intravenous magnesium for seizure prophylaxis as would otherwise be clinically indicated.

2 STUDY OBJECTIVE

2.1 Primary Objective

The primary hypothesis of this study is that amlodipine is noninferior to nifedipine ER in the management of postpartum hypertension, as evidenced by length of stay from delivery until hospital discharge. A noninferiority limit of 24 hours was selected as a clinically relevant difference.

2.2. Secondary Objective

Secondary outcomes include the need for additional antihypertensive medications (either increased dose, additional long-acting agents, or additional short-acting agents), patient-

reported side effects, medication discontinuation due to side effects, hospital readmissions, duration of breastfeeding, and breastfeeding continuation and satisfaction.

3 INVESTIGATIONAL PLAN

3.1 Study Design

This is an unmasked, pragmatic randomized controlled trial.

Women randomized to arm 1 will be started on amlodipine 2.5 mg daily. Women randomized to arm 2 will be started on nifedipine ER 30 mg daily. Dose adjustments will be made as deemed appropriate by the clinical team. Intravenous magnesium, additional long-acting antihypertensives, and short-acting antihypertensives will be administered as deemed appropriate by the clinical team. Women will be discharged from the hospital when the team feels that all discharge criteria have been met. While each provider may use slightly different discharge criteria based on their practice patterns, it is agreed upon that no patient will be discharged until her blood pressure is < 160/110 mmHg. They will be scheduled for a blood pressure check (virtual or in-person) ideally 3 to 7 days after discharge and an in-person visit ideally at 4 to 6 weeks postpartum. Participation in the study will not affect usual management aside from medication assignment.

3.2 Allocation to Treatment Groups and Blinding (if applicable)

A computer-generated randomization schedule with 1:1 allocation will be utilized. Randomization will occur at time of study enrollment utilizing REDCap. Randomization will be stratified by chronic hypertension diagnosis status. The research staff will be responsible for accessing the centralized randomization system, obtaining patient allocation, and notifying the treatment team of patient assignment.

3.3 Study Duration, Enrollment, and Number of Subjects

Study duration for each participant will last less than 8 weeks (enrollment during initial hospitalization through postpartum visit). 160 patients will be enrolled. This is anticipated to take approximately 18 months.

3.4 Study Population

English and Spanish-speaking postpartum women, who delivered at or beyond 20 weeks' gestation, with a diagnosis of chronic hypertension, gestational hypertension, or preeclampsia requiring initiation of antihypertensives.

Exclusion criteria: Use of antihypertensives antepartum, allergy to nifedipine or amlodipine, persistent tachycardia (as defined by treatment team).

4 STUDY PROCEDURES

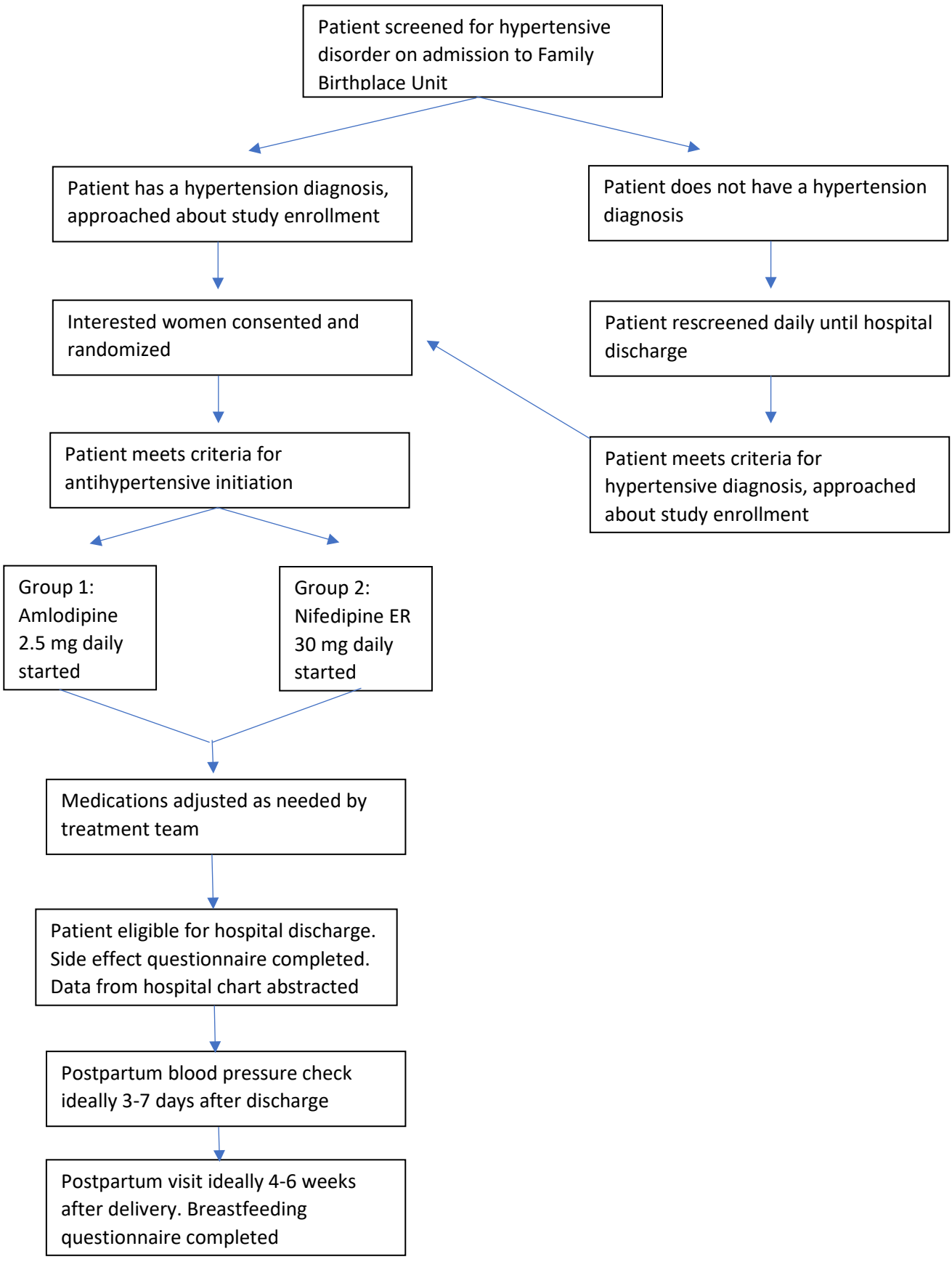
4.1 Screening procedure

Women will initially be screened for study participation at the time of admission to Greenville Memorial Hospital's Family Birthplace unit. Additionally, women who do not initially meet criteria will be rescreened daily for the development of a new hypertension diagnosis. Women will be consented for enrollment and randomized at the time of admission or at time of diagnosis to ensure maximum trial participation. Not all women who are initially consented will meet criteria for final inclusion in the study and initiation of the study drug. Based on review of historical data, approximately 50% of patients who meet diagnostic criteria will eventually meet criteria for medication administration.

4.2 Intervention

Once a woman meets inclusion criteria for antihypertensives, she will be administered the appropriate study drug. Randomization will have already occurred at the time of enrollment so that there will not be a delay in patient treatment while awaiting randomization. Randomization

will not be blinded. Women in group 1 will be started on amlodipine 2.5 mg daily and women in group 2 will be started on nifedipine ER 30 mg daily. Aside from the study drug assignment, the remainder of the patient's postpartum care will be performed according to the clinical team's discretion. Study flow is described in the below figure.


Patient screened for hypertensive disorder on admission to Family Birthplace Unit
Patient has a hypertension diagnosis, approached about study enrollment
Patient does not have a hypertension diagnosis
Interested women consented and randomized
Patient rescreened daily until hospital discharge
Patient meets criteria for antihypertensive initiation
Patient meets criteria for hypertensive diagnosis, approached about study enrollment
Group 1: Amlodipine 2.5 mg daily started
Group 2: Nifedipine ER 30 mg daily started
Medications adjusted as needed by treatment team
Patient eligible for hospital discharge. Side effect questionnaire completed. Data from hospital chart abstracted
Postpartum blood pressure check ideally 3-7 days after discharge
Postpartum visit ideally 4-6 weeks after delivery. Breastfeeding questionnaire completed

4.3 Subject Completion/Withdrawal procedures

Participants are instructed to inform their enrolling research personnel if they desire to withdraw from the study, at which point participation will be terminated.

5 STUDY EVALUATIONS AND MEASUREMENTS

-Demographic characteristics and clinical data will be abstracted from the medical chart

-Maternal age

-Gestational age at delivery

-Race

-BMI

-Parity

-Mode of delivery

-Hypertensive diagnosis

-History of diabetes (gestational or pre-gestational)

-Length of stay from delivery until discharge

-Number of acute antihypertensive treatments

-Number of dose increases of initial study drug

-Number of additional long-acting antihypertensives started

-Magnesium use

-Side effects reported

-Medication discontinuation

-Discharging physician

-Blood pressure at blood pressure check appointment

-Blood pressure at postpartum visit

-Readmissions from time of discharge until postpartum visit

-Breastfeeding status at time of postpartum visit

-Patient-reported length of breastfeeding

-Patient-reported breastfeeding satisfaction

6 STATISTICAL CONSIDERATION

6.1 Sample size calculation

An initial power calculation was performed using a standard deviation of 55.2 hours and a non-inferiority limit of 24 hours; to achieve 80% power with a 2-tailed alpha of 0.05, 66 women would be needed in each arm.

7 DATA COLLECTION AND MANAGEMENT

Data will be entered directly from the medical record into the REDCap data management system for storage and access for statistical analysis by the primary investigator.

8 REFERENCES

1. Hypertension in pregnancy: Executive summary. (2013). *Obstetrics and Gynecology, 122*(5), 1122-1131.
2. ACOG practice bulletin no. 222: Gestational hypertension and preeclampsia. (2019). *Obstetrics and Gynecology, 133*(1), e1-e25. doi:10.1097/AOG.0000000000003018 [doi]
3. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. (2019). ACOG practice bulletin no. 203: Chronic hypertension in pregnancy. *Obstetrics and Gynecology, 133*(1), e26-e50. doi:10.1097/AOG.0000000000003020 [doi]

4. Ainuddin, J., Javed, F., & Kazi, S. (2019). Oral labetalol versus oral nifedipine for the management of postpartum hypertension a randomized control trial. *Pakistan Journal of Medical Sciences, 35*(5), 1428-1433. doi:10.12669/pjms.35.5.812 [doi]
5. Magee, L., & von Dadelszen, P. (2013). Prevention and treatment of postpartum hypertension. *The Cochrane Database of Systematic Reviews, (4):CD004351. doi*(4), CD004351. doi:10.1002/14651858.CD004351.pub3 [doi]
6. Cairns, A. E., Pealing, L., Duffy, J. M. N., Roberts, N., Tucker, K. L., Leeson, P., et al. (2017). Postpartum management of hypertensive disorders of pregnancy: A systematic review. *BMJ Open, 7*(11), e018696-2017-018696. doi:10.1136/bmjopen-2017-018696 [doi]
7. Sharma, K. J., Greene, N., & Kilpatrick, S. J. (2017). Oral labetalol compared to oral nifedipine for postpartum hypertension: A randomized controlled trial. *Hypertension in Pregnancy, 36*(1), 44-47. doi:10.1080/10641955.2016.1231317 [doi]
8. Bloch, M. (2020). In Basile J. (Ed.), *Major side effects and safety of calcium channel blockers.* UpToDate.
9. Hosie, J., Bremner, A. D., Fell, P. J., James, I. G., Saul, P. A., & Taylor, S. H. (1992). Comparison of early side effects with amlodipine and nifedipine retard in hypertension. *Cardiology, 80 Suppl 1*, 54-59. doi:10.1159/000175048 [doi]
10. Naito, T., Kubono, N., Deguchi, S., Sugihara, M., Itoh, H., Kanayama, N., et al. (2015). Amlodipine passage into breast milk in lactating women with pregnancy-induced hypertension and its estimation of infant risk for breastfeeding. *Journal of Human Lactation: Official Journal of International Lactation Consultant Association, 31*(2), 301-306. doi:10.1177/0890334414560195 [doi]