**Title:** Oral Nifedipine Versus Intravenous Labetalol for Postpartum (PP) Hypertensive Emergency: A Randomized Clinical Trial (RCT)

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## 2. Proposal body

### *2.1 Specific aims*

Hypertensive disorders of pregnancy are a leading cause of maternal morbidity and mortality worldwide, with more than 50% of hypertensive related stroke and 50% of eclamptic seizures occurring in the postpartum (PP) period.[1] The American College of Obstetricians and Gynecologists recently emphasized rapid treatment of PP women to prevent complications, including the need for timely treatment of hypertensive emergencies in the PP period.[2] However, evidence-based guidelines demonstrating the optimal drug treatment regimen for PP hypertensive emergency have not been established and are desperately needed to limit catastrophic complications (e.g., eclampsia, stroke, death) in PP patients.

The primary goal during a PP hypertensive emergency is to reduce blood pressure (BP) levels. Current medication protocols call for expeditiously treating the patient within 30-60 minutes (min) of confirmed diagnosis with either: i) intravenous (IV) labetalol, which decreases peripheral vascular resistance; or ii) oral (po) short acting (SA) nifedipine, a smooth muscle relaxant. These recommendations are based on clinical trials in pregnant individuals presenting with hypertension (HTN) and suggest that po nifedipine may be superior to IV labetalol, and the outdated IV hydralazine.[3-5] However, because these guidelines were developed from data on treating hypertensive emergencies during pregnancy, the efficacy of antihypertensives in the PP period has not been validated for IV labetalol or po SA nifedipine. Importantly, the pathophysiology of PP HTN may differ from the antepartum period since there are profound fluid shifts in PP patients, causing changes in vascular tension which may alter BP drug efficacy.[6,7] It is unknown which antihypertensive is most effective at quickly normalizing BP in the PP period and which drug is best to manage care in the days after an emergency hypertensive event.

Our small retrospective analysis of 104 PP individuals presenting with a hypertensive emergency at Columbia University Irving Medical Center (CUIMC) found that both IV labetalol and po SA nifedipine are effective options for controlling PP severe HTN. However, patients who received po SA nifedipine required fewer doses of medication with less frequent crossover to another antihypertensive agent. While these results seem promising, we do not know why patients were assigned specific medications, or the time trajectory of BP reduction from drug administration to control BP, a key metric for identifying how efficiently a drug reduces BP.

Additionally, the retrospective study did not consider that any patient undergoing antihypertensive treatment during the first 24 hours of a PP emergency concurrently receives IV magnesium sulfate to prevent seizures. The coadministration of these drugs is significant since recent research suggests that the combination of magnesium with some antihypertensives (e.g., nifedipine) may have a synergistic effect to more quickly lower BP.[8]

**The overall goal is to conduct a prospective randomized open-label controlled trial to determine:**

**1)** which standard antihypertensive treatment regimen optimally treats PP hypertensive emergencies and
**2)** how synergistic effects with magnesium sulfate impact PP BP control.

**Aim 1. To determine whether po nifedipine or IV labetalol better treats a hypertensive emergency in PP women.** *Hypothesis 1a*. Compared with IV labetalol, po SA nifedipine will have

a shorter time interval (min) to achieve a therapeutic BP goal. *Hypothesis 1b.* Compared with IV labetalol, po SA nifedipine will result in a lower incidence of need for use of an alternative antihypertensive therapeutic agent.

**Aim 2. To investigate the effect of withdrawal of magnesium sulfate on antihypertensive therapies in severe PP HTN.** *Hypothesis 2*. Administration of po SA nifedipine will result in a higher incidence of rebound HTN in the 12 hours after magnesium is discontinued, compared to IV labetalol.

**Exploratory Aim:** We will compare BP trajectories after initiation of magnesium, stratified by treatment arm, within the first 36 hours from randomization to discharge.

**Public Health Impact:** The data from this study will determine which standard of care medication is most effective antihypertensive regimen during control of an initial hypertensive emergency and during the first 24 to 36 hours following the initial BP control event; this will inform clinical guidance for treatment algorithms for PP hypertensive emergencies. Further, an optimized antihypertensive medication regimen may be associated with improved maternal morbidity outcomes and safety, reduced lengths of maternal hospitalization, and decreased need for readmission in the PP period. Thus, this research project has potential to improve clinical practice in the short term and generate a body of research evidence which will serve as the foundation for future studies testing treatment algorithms to guide BP treatment decisions for PP patients. ***In addition, this research project provides a framework for me to execute my career development goals, including application of learned clinical research methods, deepening an expertise in cardiovascular disease, building and utilizing interdisciplinary networks and advancing my career in academic medicine through leadership and dissemination of research findings.***

### *2.2 Background*

Although the exact incidence of PP hypertension is unknown, devastating sequelae- including maternal stroke, seizure and death[6]- are increasingly recognized in the PP period. Recent studies have demonstrated that in women who sustained hypertensive related stroke, more than 50% were in the PP period.[7] Additionally, eclampsia may be most common in the PP period, with up to 50% of seizures occurring initially PP, most often within 48 hours of delivery.[8,9] Because of this, there is a general consensus that a hypertensive emergency in the PP period should be treated expeditiously, as defined by within 30-60 minutes of confirmed diagnosis.[10] However, there is no consensus on *which* antihypertensive agent most rapidly achieves target BP.

Several studies have compared the efficacy of antihypertensives in the acute management of hypertensive emergencies in pregnancy.[11-16] These studies provided evidence that po nifedipine may be superior to IV hydralazine or IV labetalol.[12-14] However, these findings were suggested with use in the antepartum period. The pathophysiology of PP hypertension is thought to be uniquely related to profound fluid shifts in the peripartum period secondary to a rise in intravascular volume related to mobilization of extravascular fluid.[17,18] For this reason, the efficacy of antihypertensives in the PP period may differ. There is also plausibility for differential effect by race. The non-pregnant medical literature has demonstrated that calcium channel blockers (CCB) to be more effective in Black patients.[19] Consequently, the National Institute for Health and Clinical Excellence clinical practice guidelines for hypertension recommend CCB as the initially therapy.[20]

Only one study has solely looked at acute managing hypertensive emergencies in the PP period.[11] This prospective randomized controlled trial compared the efficacy of IV labetalol to IV hydralazine. They found no difference in what they defined as successful lowering of BPs (systolic<160 mm Hg and/or diastolic<110 mm Hg) with 1 to 5 doses of a single antihypertensive. There are several limitations with these findings. First, although IV hydralazine has long been considered a first-line medication, a recent systematic review has suggested a higher side effect profile.[21] Second, a dilemma exists in how to transition a patient to po medication after parental medication. Third, incidence of the primary outcome, persistent severe hypertension, was very low, therefore medication superiority in this clinical context could not be properly assessed.

Therefore, a knowledge gap exists on what antihypertensive is most effective in the PP period in acutely treating hypertensive emergencies. Our objective is to assess which antihypertensive (po nifedipine or IV labetalol) results in shorter time interval required to achieve a therapeutic BP goal (systolic<160 mm Hg and/or diastolic <110 mm Hg). This study provides a unique opportunity to better understand the complex interaction between antihypertensives specifically in the PP period.

### *2.3 Methods*

We hypothesize that among patients with a PP hypertensive emergency (BP systolic ≥160mmHg and/or diastolic ≥110mmHg, on two occasions 15 minutes apart), po nifedipine will be superior to IV labetalol in acutely lowering BP, and response to medication may be differential by maternal race. This will be a prospective randomized open-label controlled trial designed to examine the difference between po nifedipine and IV labetalol in the time to achieve a therapeutic BP goal (systolic<160 mm Hg and/or diastolic <110 mm Hg) in the PP period.

*Algorithm for management of hypertensive emergencies*

The algorithm for the management of hypertensive emergencies in pregnancy directs decision making based primarily on clinical trials done on patients in the antepartum period.[12-16] This protocol is supported by expert opinion[1] but has not been validated in the PP setting. Since half of patients with hypertensive emergencies present in the PP period, this protocol has the potential to meaningfully improve outcomes and reduce liability exposure if validated. The goal of the protocol is to establish which medication is superior in acutely lowering BP in the PP period. There are three specific aims of the proposed project that will assess medication superiority: 1) Examining the necessary time to achieve target BP in managing PP hypertensive emergencies in po nifedipine versus IV labetalol, 2) Evaluate which medication achieves better sustained BP control and 3) Assess whether there are racial or ethnic differences in both response to medication and ultimate BP control.

*Inclusion criteria*

- Patients admitted to labor and delivery (L&D) with severe range BP, defined as a systolic ≥160 mm Hg and/or diastolic ≥110 mm Hg
- Postpartum, immediately to 6 weeks postpartum
- With a prior diagnosis of chronic hypertension (not on medication) or hypertensive disorder of pregnancy

*Exclusion criteria*

- They may not have previously had exposure to either study medication within the previous 24-hour period.
- Patients with a known atrial-ventricular heart block or moderate to severe bronchial asthma will be excluded, or other contraindication to receiving either study medication.
- Patients with heart rate of <60 beats per min.

### *2.3.1 Study Procedures*

Eligible patients will be recruited from the L&D as well as the antepartum and postpartum units at Columbia University Irving Medical Center. In terms of screening, those with an ACTIVE DIAGNOSIS of one or two severe range blood pressures, who will likely require treatment will be approached.

The patients with ACTIVE DX, will be identified based on the following screening modalities:

- Patients who are postpartum who have one or two severe range blood pressures. These patients will be on L&D, the PP floor, triage unit on L&D and the ED.

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After the first severe range BP is taken, about 15 minutes later a second blood pressure will be taken. This is done by the patient's clinical team and follows standard of care protocol. If this second BP is severe range, they will receive the study medication that they were randomized to. Both medications are considered standard of care for treating a hypertensive emergency in pregnancy, defined as systolic ≥160 mmHg and/or diastolic ≥110 mmHg on two or more occasions, 15 minutes apart. BP measurements will be with the standard of care non-invasive sphygmomanometer blood pressure monitoring cuff device that is used to take care of all patients in this setting, as well as the continuous BP monitor.

**Randomization process**

Based on persistent limitations of recruitment for this study we are implementing a change to the study design to be a single institutional cross over study. In this method, starting at the first day of each month all postpartum patients who have a hypertensive emergency, require short acting medication, and do not have any contraindication to either of the study medications will receive medication A (short acting oral nifedipine). This will continue every day until the end of the month. Starting at the first day of the next month, all postpartum patients who have a hypertensive emergency, require short acting medication, and do not have any contraindication to either of the study medications will receive medication B (IV labetalol). This will continue each month in a 1:1 ratio until enrollment has been achieved.

*Study design*

We will perform a single institutional randomized cross over study, open-label trial including women with a diagnosis of a hypertensive emergency in the PP period.

*Sample size and statistical power*

The primary exposure will be antihypertensive medication (oral SA nifedipine or IV labetalol) and the primary outcome will be time (minutes) to achieve a therapeutic BP (<160 mmHg systolic and <110 mmHg diastolic). We will assess if there is difference in the number of min between those patients who receive nifedipine versus labetalol in time to achieve a therapeutic BP goal, as ACOG has emphasized rapid treatment of pregnant and PP women to prevent complications. The only studies in the literature comparing time to BP control in pregnant women was during the antepartum period. However, these studies were small and conducted outside of the US with different BP parameters. In a study on 120 patients with severe hypertension in pregnancy, Zulfeen et al.(2019) showed that the mean time taken to achieve the target BP in the labetalol

group was higher (37.75 min) than in the nifedipine group (27.25 min) [mean difference 9.5 min, p=0.002].[21] The nifedipine group also required significantly lower doses (1.82±0.83) as compared to the labetalol group (2.45±1.32) [p=0.002]. Nifedipine was 1.8 times more likely to achieve targe BP (Hazard Ratio = 1.8). Based on these data, with an alpha of 0.05 and 80% power, approximately 52 patients will be required in each group to show a similar difference in BP control. With the assumption that 5% of patients are lost to follow-up, the required sample size would be a total of 104 patients.

*Statistical Analysis*

For Aim 1a, with the primary exposure as the randomized antihypertensive medication (oral SA nifedipine or IV labetalol) and the primary outcome as the time to BP control (in minutes), we will assess if there is a difference in the number of minutes between those patients who receive nifedipine versus labetalol in time to achieve a therapeutic BP goal. The analysis will also include assessing survival outcomes in each treatment arm (Kaplan-Meier, log-rank). Additionally for Aim 1b, we will analyze which of the two study medications result in a lower incidence of need for use of the alternative antihypertensive therapeutic agent (Logistic regression). For Aim 2, we will compare the two study medications to determine which has a higher incidence of rebound HTN - defined by reoccurrence of severe HTN (Logistic regression). For our exploratory aim, we will compare BP trajectories after initiation and cessation of magnesium, stratified by treatment arm within the first 36 hours from initial randomization to discharge from the hospital. We will use a linear mixed model for repeated measures to analyze the BP trajectories over time, adding nifedipine, labetalol and magnesium into the model as covariates. For other secondary outcomes normally, distributed continuous data will be analyzed with Student's t-test for numerical data and Chi square/Fisher's exact test for categorial data. All tests will be two sided and a p-value of <0.05 will be considered statistically significant. Patients will be analyzed on an intention-to-treat basis.

### *2.4 Outcome Measures*

For specific aim number 1 the primary outcome will be time (minutes) interval required to achieve the therapeutic BP goal of <160 mmHg systolic and <110 mmHg diastolic.

For specific aim number 2, secondary outcomes will be included (i) the number of times a patient has recurrence of severe hypertensive necessitating treatment with an antihypertensive and (ii) the need to use a second (alternative) antihypertensive medication.

### *2.5 Significance*

Due to the significant maternal morbidity and mortality and the disparities in this mortality resulting from hypertensive emergencies, in January 2019 obstetric leadership published the first even practice bulletin with a proposed algorithm for standardized management of treating severe BP.[5] And while the algorithm is based on a synthesis of available evidence and expert opinion, research has not validated its usefulness. In addition to a lack of evidence-based research demonstrating superiority of antihypertensives in the PP period, several other important considerations have not been addressed. First, many patients present with hypertensive emergencies with without IV access. An oral medication like nifedipine can be readily administered upon confirmation of a hypertensive emergency. Further, oral medications are less expensive than parenteral therapy. Additionally, the bioavailability of intravenous and oral medications may vary, and conversion to oral therapy may be unpredictable with possibility of prolonged hospital stay and readmissions, both increasing healthcare costs significantly. For all

of these reasons, the World Health Organization (WHO) recognizes that the ideal route of administration of any medication be oral.[24]

Providing evidence for treating postpartum patients would represent practice changing evidence that may improve maternal outcomes, improve safety, reduce cost and disparities, and direct further refinements in clinical management. Thus, this research project has potential to improve clinical practice in the short term, and lead to a body of research evidence in the future.

*Results from this project aid in application for future studies*

Hypertensive disorders of pregnancy disproportionately affect non-white patients. In particular Black women with preeclampsia are at higher risk for severe morbidity and mortality.[25] While evidence supports that timely administration of antihypertensives may be associated with decreased risk for stroke, it is still unclear what medications may be most effective in Black patients. Given the disproportionate morbidity and mortality associated with hypertensive disease in pregnancy in Black patients, there is an urgent need for more definitive data on the real-world therapeutic effectiveness of antihypertensives in this subset of patients at increased risk.

This clinical project will provide preliminary data to better expand on the knowledge gap of optimal BP management in Black and Hispanic patients.

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