Nifedipine XL versus placebo for the treatment of preeclampsia with severe features during induction of labor

Protocol Proposal

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1.0 Introduction

1.1 Study Abstract

Preeclampsia occurs in 5-8% of pregnancies and is associated with significant maternal and neonatal morbidity and mortality.[1] Diagnosis of preeclampsia with severe features requires delivery when the diagnosis is made at or beyond 34 weeks gestation. Delivery may be indicated prior to 34 weeks when criteria for expectant management are not met, such as in the setting of uncontrolled maternal hypertension, progression of disease with worsening of laboratory values or persistent clinical symptoms, or worsening fetal well being. Although clear algorithmic guidelines exist for the treatment of acute-onset severe hypertension in the antepartum, intrapartum or postpartum period[1], limited data exists on starting long acting antihypertensive medications to aid in management of elevated blood pressures during induction of labor.

1.2 Primary Aim

To compare Nifedipine 30mg XL with placebo for improved blood pressure control in women with preeclampsia with severe features undergoing induction of labor.

1.3 Primary Hypothesis

Among women with preeclampsia with severe features undergoing induction of labor, Nifedipine 30mg XL decreases need for additional acute antihypertensive treatment compared with placebo.

1.4 Secondary Aims

The secondary aims of this study are to assess the effect of Nifedipine 30mg XL compared with placebo on mode of delivery, indications for cesarean delivery, maternal hypotension and other adverse events, and a composite of maternal and perinatal adverse outcomes.

2.0 Background

Preeclampsia complicates approximately 1 in 25 pregnancies[2], and is therefore a relatively common obstetric complication. It is the second leading cause of maternal mortality worldwide after hemorrhage, and may lead to maternal comorbidities including stroke, eclampsia, and organ failure. Fetal or neonatal outcomes include intrauterine growth restriction, low birth weight, and stillbirth. Many of the complications associated with preeclampsia lead to early induction of labor or cesarean delivery and subsequent preterm birth.

Preeclampsia with severe features may be diagnosed in the absence of severe blood pressures, defined as systolic blood pressure (SBP) ≥160mm Hg or diastolic blood pressure (DBP) ≥110mm Hg, when other severely defining features are present. These include clinical features (persistent headache or vision disturbances), laboratory features (liver enzymes twice the upper limit of normal, thrombocytopenia with platelet count less than 100,000/mL, or creatinine greater than 1.1mg/dL, or end organ injury. When severe blood pressures are present, prompt management is required to avoid sequelae such as stroke or placental abruption. Existing data support the use of oral Nifedipine or intravenous hydralazine or labetalol for the treatment of hypertensive urgency in pregnancy[1]. Optimal treatment for severe blood pressure during induction of labor for the diagnosis of preeclampsia with severe features has not been described, but inadequate blood pressure control is a risk factor for cesarean

delivery. In a review of the Consortium for Safe Labor, at least 27% of women undergoing induction of labor for preeclampsia with severe features between 24-34 weeks gestation required a cesarean delivery for hypertensive disease[3]. In a review of over 200,000 women using the Prospective database, the frequency of any antihypertensive use in preeclampsia increased between 2006 and 2014, with corresponding risk reduction in stroke[4].

Acute blood pressure treatment is not without maternal or fetal risk. In about 10% of pregnant patients treated with intravenous labetalol or hydralazine, hypotension (defined as a drop in 30% of SBP) occurs[5]. Rapid and profound decrease in maternal blood pressure may result in hypoperfusion of the uterus secondary to a rightward shift occurring in the pressure autoregulation curve of the uterine arteries[6], whereas a gradual decrease in blood pressure is safer for both the patient and the fetus, with less risk for maternal dizziness or fetal distress. When a non-reassuring fetal monitoring cannot be adequately resuscitated through maternal volume expansion, repositioning, or improvement in blood pressure, cesarean delivery is indicated.

In the antepartum or postpartum period, the most commonly prescribed oral agents for maintenance therapy include labetalol, methyldopa and Nifedipine. Scant guidelines exist on the introduction of a maintenance or long-acting agent anti-hypertensive medication to control blood pressure during an induction of labor. A recent randomized controlled trial compared oral nifedipine, labetalol and methyldopa in women with severe hypertension, with the primary outcome of non-severe blood pressure at 6 hours after administration of first dose, more common in patients assigned to Nifedipine[7]. In this study, the median time to delivery among all participants was 24 hours, with cesarean delivery for the indication of uncontrolled blood pressure occurring least frequently with Nifedipine (absolute difference of -5.2 compared to labetalol and -3.5 compared to methyldopa).

We propose a randomized double blind placebo controlled trial in women with preeclampsia with severe features undergoing induction of labor, to evaluate the efficacy of Nifedipine XL initiated in the intrapartum period on the need for acute therapy to reduce persistently severe range blood pressure.

2.1 Rationale for a Randomized Controlled Trial

The lack of existing data on optimal hypertension management during induction of labor for preeclampsia with severe features leads to confusion among providers and significant variation in management. Exhausting the algorithms for intravenous labetalol and hydralazine, as well as oral immediate-release nifedipine, necessitates consideration of a continuous infusion of an anti-hypertensive agent, often requiring ICU-level care. Furthermore, intravenous therapy also introduces the risk for cesarean due to non-reassuring fetal status secondary to maternal hypotension. Therefore, patients with persistently severe range blood pressures are at risk for multiple intravenous or immediate-acting oral agents, as well as at risk for cesarean delivery to expedite treatment of preeclampsia.

To further describe best practice management of intrapartum preeclampsia with severe features, we aim to compare long-acting nifedipine 30mg to placebo. This dose will allow full range of options with intravenous labetalol or hydralazine, as well as immediate-release Nifedipine, for the treatment of hypertensive urgency.

3.0 Study Design

This is a randomized double blind placebo controlled trial comparing Nifedipine 30mg XL to placebo in 110 patients after decision has been made to proceed with induction of labor for the diagnosis of preeclampsia with severe features.

Potential study participants will be identified at the time of admission to the labor & delivery unit. Eligibility criteria will be verified. At the time of enrollment, patients will be randomized to either the study drug (oral Nifedipine XL 30mg) or identical placebo. Participants will receive the first dose of the study medication after enrollment unless recorded blood pressure is <120/70. Dosing will continue every 24 hours through delivery. Algorithms for the administration of intravenous labetalol or hydralazine will be utilized by the primary provider at his or her discretion. Postpartum management of hypertension with oral medications will be unblinded and at the provider's discretion.

This study is a randomized, double-blind, placebo controlled single center clinical trial conducted at The Ohio State University Wexner Medical Center, where approximately 216 women are delivered for preeclampsia with severe features each year. These women will be randomized at the time of induction of labor into two groups.

- Oral administration of 30mg Nifedipine XL q24 hours until delivery
- Matching placebo group q24hrs until delivery
- Women may take the study drug/placebo concurrently with intravenous labetalol or hydralazine or immediate release Nifedipine for the treatment of severe blood pressures during cervical ripening and/or induction of labor per unit protocol.
- All other obstetric care will be at the discretion of the primary provider, including but not limited to cervical ripening and augmentation methods, intrapartum resuscitation, IV magnesium for seizure prophylaxis and recommendations regarding mode of delivery. Data will be collected on these components of routine obstetric care. Analysis will be by intent to treat.

3.1 Preeclampsia with severe features diagnosis determination

Among women without a history of chronic hypertension, preeclampsia without severe features is typically made based on elevated blood pressures and proteinuria greater than 300mg/24 urine collection; however, in the absence of proteinuria, the severely-defining features below can be used for diagnostic purposes. Preeclampsia with severe features is diagnosed based on the following:

- Development of hypertension, defined as a persistent SBP of 160mm Hg or higher, or DBP of 110mm Hg or higher on two occasions at least 4 hours apart while the patient is on bedrest (unless antihypertensive therapy is initiated before this time)
- Alternatively, the diagnosis can be made with a SBP of 140 mm Hg or higher, or a DBP of 90 mm Hg or higher after 20 weeks of gestation in a patient with previously normal blood pressure, plus any of the following:
    - Thrombocytopenia, with platelet count of less than 100,000/microliter
    - Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, or both
    - Progressive renal insufficiency (serum creatinine concentration greater than 1.1mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
    - Pulmonary edema
    - New-onset cerebral or visual disturbances

- In women with baseline chronic hypertension, preeclampsia is diagnosed based on any of the following (not accounted for by alternative diagnoses):
    - Severe hypertension (SBP ≥160 mmHg or DBP ≥110 mmHg) ≥ 20 weeks in gestation on two occasions with measurements taken at least 4 hours apart or 1 occasion with subsequent antihypertensive therapy, or an escalation of antihypertensive medications to control blood pressure
    - New onset of proteinuria or a doubling in protein in women with baseline proteinuria
    - Thrombocytopenia (platelet count <100,000 per microliter)
    - Progressive renal insufficiency (serum creatinine >1.1 mg/dl or doubling of the serum creatinine in the absence of other renal disease)
    - Impaired liver function (elevated transaminases ≥ 70 U/L, or severe persistent right upper quadrant or epigastric pain unresponsive to medication)
    - Pulmonary edema diagnosed clinically by exam or chest x-ray
    - New-onset and persistent (non-responsive to supportive treatment) cerebral or visual symptoms.
    - HELLP [hemolysis, elevated liver enzymes and low platelet count] syndrome defined as the occurrence of all of the following (not accounted for by alternative diagnoses):
    - Hemolysis: evidenced by (1) serum total bilirubin ≥ 1.2 mg/dL (20 µmol/L), (2) serum lactate dehydrogenase (LDH) ≥ 600 IU/L, or (3) hemolysis on peripheral smear
    - Thrombocytopenia (platelet count < 100,000 / microliter)
    - Serum aspartate aminotransferase (AST) or alanine transaminase (ALT) ≥ 70 IU/L
- Atypical HELLP defined as the occurrence of 2 of the 3 following (not accounted for by alternative diagnoses)
    - Hemolysis: evidenced by (1) serum total bilirubin ≥ 1.2 mg/dL (20 µmol/L), (2) serum lactate dehydrogenase (LDH) ≥ 600 IU/L, or (3) hemolysis on peripheral smear
    - Thrombocytopenia (platelet count < 100,000 / microliter)
    - Serum aspartate aminotransferase (AST) or alanine transaminase (ALT) ≥ 70 IU/L

Eclampsia defined as an occurrence of a seizure without any known cause

3.2 Study Aims

The primary aim is the need for intravenous or immediate-release oral therapy for acute treatment of severe hypertension.

3.3 Secondary Aims

The secondary aims of this study are to evaluate

- Route of delivery
- Indications for cesarean section (uncontrolled hypertension, failure to progress, non-reassuring fetal well-being, etc)
- Maternal hypotension (<30% baseline or mean arterial pressure <65 mmHg)

- Time from enrollment to hospital discharge
- Postpartum hypertension control, including frequency and dosing of acute or maintenance antihypertensive therapy
- Composite of adverse maternal outcomes (time duration to need for acute antihypertensive therapy, receipt of second dose study drug, time from randomization to delivery, seizure, adverse CNS outcome (stroke or cortical blindness), pulmonary edema, oliguria, DIC, admission to ICU, dialysis, mechanical ventilation, abruption, post-partum hemorrhage, receipt of blood products, maternal death)
- Composite of adverse neonatal outcomes (intrapartum fetal demise, abruption, neonatal death, Apgar score <7 at 5 minutes, intubation, convulsions, IVH, confirmed sepsis, RDS requiring O2, NICU admission)

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3.4 Study Groups

This study is a randomized, double-blinded placebo controlled single center clinical trial conducted at OSU Wexner Medical Center of 110 women with diagnosis of preeclampsia with severe features. These women will be randomized at the time of admission to the labor & delivery unit to one of two groups:

- Daily Nifedipine 30mg XL
- Identical appearing placebo

Participants in the study will have the study medication administered by their nurse at time of enrollment and randomization, and every 24 hours thereafter until delivery. All other obstetric care will be at the discretion of the primary provider, including but not limited to: treatment of hypertensive urgency, timing and mode of delivery. Data will be collected on these components of routine obstetric care.

3.5 Population and Eligibility Criteria

a) Setting: This single center study will be conducted at The Ohio State University Wexner Medical Center.

b) Inclusion criteria:

1. Women aged 18-45 with a viable single or twin intrauterine pregnancy between 22 0/7 and 41 6/7 weeks gestation based on the best obstetric estimate by ACOG criteria.

2. Diagnosis of preeclampsia with severe features with decision made to induce labor. The patient may or may not have already received acute treatment for severe blood pressures.

c) Exclusion criteria:

- Known allergy or adverse reaction to Nifedipine or any medical condition where Nifedipine is contraindicated, such as galactose intolerance, severe GI stricture, and GI hypomotility disorder.
- Currently receiving Nifedipine XL as part of hypertension management prior to induction of labor
- Participation in another trial that affects the primary outcome without prior approval
- Physician/provider or patient refusal

- Participation in this trial in a prior pregnancy
- Triplet or higher order pregnancy

3.6 Gestational Age Determination

Gestational age is determined using criteria proposed by the American Congress of Obstetricians and Gynecologists, the American Institute of Ultrasound in Medicine, and the Society for Maternal-Fetal Medicine, and is denoted “project gestational age.” The “project EDC,” which is based on the project gestational age, cannot be revised once a determination has been made. If the pregnancy is conceived by in-vitro fertilization, project gestational age is calculated from the date of embryo transfer and the embryo age at transfer. If the pregnancy is conceived spontaneously (including ovulation induction and artificial insemination) information from the earliest dating ultrasound and the last menstrual period are used to determine project gestational age. If no dating ultrasound has been performed previously, one must be performed before the patient can be randomized.

The following algorithm is used:

- The first day of the last menstrual period (LMP) is determined, and a judgment made as to whether or not the patient has a “sure” LMP date.
- If the LMP date is unsure, ultrasound measurement(s) obtained at the patient’s first dating ultrasound examination is used to determine the project gestational age. If the first dating ultrasound was conducted before 14 weeks 0 days, the measurement must be based on crown rump length (CRL).
- If the LMP date is sure, project gestational age is determined by a comparison between the ultrasound measurements based on the earliest dating ultrasound. If the ultrasound confirms the gestational age by LMP as in the table below, the LMP-derived gestational age is used to determine the project gestational age. Otherwise, project gestational age will be determined based upon the ultrasound measurement.

Table 1. Cutoffs for using LMP to determine gestational age for sure LMP

Gestational age at first ultrasound by LMP	**Ultrasound agreement with LMP**
up to 8 6/7 weeks (by CRL)	≤5 days
9 0/7 weeks to 13 6/7 weeks (by CRL)	≤7 days
14 0/7 to 15 6/7 weeks	≤7 days
16 0/7 to 21 6/7 weeks	≤10 days

**CRL = Crown Rump Length*

3.7 Randomization Method and Masking

Randomization may occur upon confirmation that all inclusion/exclusion criteria are satisfied, after verification of participant consent and HIPAA authorization.

Consenting women will be randomly assigned to nifedipine 30XL and placebo in a 1:1

ratio according to a randomization sequence prepared by and maintained by independent statistician and available from central investigational pharmacy who will dispense study drug or placebo. The two study arms are double masked; neither the patient nor the clinical staff will be aware of the treatment assignment.

The simple blocked randomization method will be used to generate the randomization sequences because it provides a high probability of balance in treatment assignments, it is unpredictable, and it allows an explicit randomization analysis to be conducted with relative ease.

4.0 Study Procedures

4.1 Screening and Eligibility and Consent

The participant's inclusion and exclusion criteria will be verified as will her interest in the study. The informed consent process will be conducted by trained research staff and will include all aspects of the study and a full disclosure of the risks, benefits, procedures, and alternatives. The study consent and HIPAA authorization will be signed after all questions have been discussed and answered. Collection of baseline information, including contact information, demographic and pregnancy history information, will follow the informed consent process.

4.2 Randomization and Baseline Visit Procedures

Randomization may occur upon confirmation that all inclusion/exclusion criteria are satisfied, after verification of participant consent and HIPAA authorization. Study staff will also verify participant contact information and obtain a Release of Information, as permitted by local policy, to collect outcome and serious adverse event (SAE) documentation. Patients will be assigned next sequential number and central pharmacy will dispense study drug or placebo depending on randomization allocation sequence.

Once the patient is randomized, the patient will receive a study drug or placebo from clinical nurse. She will be instructed to take 1 pill daily until delivery.

In addition to information collected for eligibility, gestational age, and EDC determination, the following information will be obtained at randomization from a patient interview followed by a review of her chart:

- Demographic information: age, race, insurance status
- Medical history: pre-pregnancy weight, current weight, height, chronic disease history
- Obstetrical history including outcomes of all prior pregnancies and which pregnancy(ies) was complicated by preeclampsia.
- Social history: marital status, years of education, alcohol use, tobacco use, and maternal drug use
- Record baseline blood pressure, and baseline preeclampsia laboratory data including platelets, creatinine, liver function tests and proteinuria status, if performed
- Medication use e.g. ASA prior to enrollment, antihypertensive medications including prior administration of acute antihypertensive medications, metformin, anti-platelet agents, etc

4.3 Obstetric Management

All aspects of obstetric management will be left to the patient's provider. Data will be collected on baseline laboratory values (when obtained), surveillance ultrasounds for fetal growth, antenatal testing, and timing and mode of delivery.

5.0 Sample Size and Power

For the purposes of sample size estimation, it is assumed that 85% of women with diagnosis of preeclampsia with severe features receive acute IV antihypertensive therapy and 74% will require additional IV hypertensive therapy throughout induction of labor process. Assuming rate of additional acute IV antihypertensive (primary outcome) without use of maintenance long acting antihypertensive therapy is 74%. It is estimated that sample size of 110 women is required to demonstrate at least a 40% reduction in use of additional acute antihypertensive therapy with the use of nifedipine 30XL (from 74% to 44%), with a power of 80%, and type I error of 5% 2-sided.

Primary Outcome		Treatment Effect	Power	Total N
Placebo	Nifedipine			
75%	52.5%	30% reduction	80%	140
			85%	160
			90%	188
	45%	40% reduction	80%	82
			85%	92
			90%	108
70%	49%	30% reduction	80%	170
			85%	194
			90%	226
	42%	**40% reduction**	80%	97
			85%	**110**
			90%	128
65%	45.5%	30% reduction	80%	202
			85%	230
			90%	270
	39%	40% reduction	80%	114
			85%	130
			90%	150

2.6 Statistical Analysis Plan

Standard comparisons of characteristics between groups will be conducted at baseline. It

is anticipated that the randomization scheme will balance the groups for these covariates and they will not be adjusted for in the primary analysis.

The primary analysis will compare incidence of the outcome between the 2 study groups. If the two groups show a difference in the incidence of the primary outcome, interactions will be evaluated and subgroup analyses conducted to determine whether the effect prevails.

Lost to follow up should not occur given study design and no follow up is scheduled. Since many of the secondary endpoints as dichotomous variables like the primary outcome, standard statistical methods for rates and proportions will be appropriate. Continuous variables will be compared using standard statistical methods,

6.0 Data Management

6.1 Data Collection Forms

Data will be collected on standardized forms on which nearly all responses have been pre-coded. Each form is briefly described below.

- Screening Log
- Eligibility Checklist
- Randomization: completed for all eligible women, lists randomized drug code number
- Baseline Form: includes detailed demographic and social data, medical & obstetrical history, and current pregnancy complications (to date), as applicable
- Study Drug lots: documents dispensing of study medication and the return of any unused study medication
- Maternal delivery and outcome forms: documents labor, delivery and postpartum information through the first 7 days after delivery
- Neonatal baseline form: records date and time of birth, delivery data and status at delivery for each fetus/infant
- Neonatal outcome form: records outcome data for all infants admitted to the NICU or special care nursery
- Patient status form: documents loss to follow-up/withdrawal status, side effects since the last dose
- Will do an intrapartum BP log.

6.2 Recruitment and Data Collection Period

Over 200 women are diagnosed with preeclampsia with severe features at Ohio State Wexner Medical Center. Based on inclusion criteria it is estimated that at least 60% of women would meet inclusion criteria and undergo an induction of labor (n=120). Using a conservative 60%, 72 women per year would be eligible and consent for enrollment. Therefore this study can be completed in less than 2 years.

1. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstet Gynecol 2019; 133:1.
2. Ananth CV, Keyes KM,Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. BMJ. 2013;347:f6564.
3. Coviello EM, Iqbal SN, Grantz KL, et al. Early preterm preeclampsia outcomes by intended mode of delivery. Am J Obstet Gynecol 2019;220:100.e1-9.
4. Cleary KL, Siddiq Z, Ananth CV, Wright JD, Too G, D'Alton ME, Friedman AM. Use of Antihypertensive Medications During Delivery Hospitalizations Complicated by Preeclampsia. Obstet Gynecol. 2018 Mar;131(3):441-450.
5. Sharma, Kathryn J., Rodriguez, Maria, Kilpatrick, Sarah J., Greene, Naomi, Aghajanian, Paola. Risks of parenteral antihypertensive therapy for the treatment of severe maternal hypertension are low. Hypertension in Pregnancy 2016: 35:1, 123-128\
6. Magee LA, Cham C, Waterman EJ, Ohlsson A, vonDadelszen P. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. Br Med J 2003;327:1-10.
7. Easterling, Thomas, Mundle, Shuchita, Bracken, Hillary, Parvekar, Seema, Mool, Sulabha Magee, Laura A, von Dadelszen, Peter, Shochet, Tara, Winikoff, Beverly. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. Lancet 2019; 394: 1011–21.