Use of Nitrous Oxide Donor for Labor Induction in Women with PreEclampsia (NOPE)

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Use of Nitrous Oxide Donor for Labor Induction in Women with PreEclampsia or Gestational Hypertension (NOPE): A Randomized Controlled Trial

Draft Protocol

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1. Introduction

1.1 Background:

Hypertensives diseases of pregnancy, including preeclampsia and gestational hypertension affects at least 5-10% of all pregnancies. Preeclampsia is the most severe form and is a rapidly progressive condition characterized by high blood pressure and the presence of protein in the urine. Gestational hypertension is defined as systolic blood pressure (SBP) >140 mmHg and diastolic blood pressure (DBP) >90 mmHg and approximately half of women diagnosed with gestational hypertension will progress to preeclampsia.

To date there is no cure for preeclampsia except delivery. Given the potential of adverse consequences for both mother and fetus, preeclampsia and gestational hypertension is the leading diagnosis triggering medically indicated preterm birth. Therefore, most patients with gestational hypertension or preeclampsia who require delivery will not be in spontaneous labor and must undergo induction of labor. The obstetrician then faces a dilemma regarding the optimal method of induction. As to date there is no consensus to guide the physician on the best method for induction of labor. The ideal induction agent(s) should result in a relatively short induction to delivery interval without risk to fetus and with low rates of cesarean sections. The induction to delivery interval and low rates of CD is especially important in preeclampsia, to minimize significant maternal and infant morbidity associated with CD and to preventing worsening of disease.

Nitric oxide (NO) is a free radical that plays a fundamental role in human physiology, being involved in the homeostasis of different functions. In obstetrics, this molecule is determinant in the physiology of labor and cervical ripening and it has been implicated as playing a fundamental role in the etiology of preeclampsia. In blood vessels, NO is a potent vasodilator and platelet-aggregation-inhibitor. It has been postulated that lack of NO during gestation is related to the development of gestational hypertension and preeclampsia. Studies investigating the replenishment of NO in preeclampsia have shown improvements in blood pressure, uterine artery pulsatility index (which is classically abnormally high in preeclampsia), and a reduction in platelet activation.

Another proven role of NO, is induction of the physiological process of cervical ripening. Compelling animal data showed that all known Nitric-Oxide Synthase isoforms (iNOS, nNOS, eNOS) were present in the cervix. An increase in iNOS occurred during labor at term compared with early gestation. In rats, during preterm labor, iNOS concentrations increased significantly in the cervix. Labor duration was significantly prolonged when NOS was inhibited by L-NAME. Furthermore, cervical extensibility decreased significantly after in-vitro incubation with L-NAME. Overall, the above experimental data suggests NO system plays an active role in the cascade of processes involved in preparing the uterus and cervix for parturition, and its administration can speed the process of cervical dilatation.

Human cervical tissues display the same augmentation of iNOS, in women approaching term. NO-production in the cervix is low during gestation and becomes upregulated once pregnancy advances to term. Vaginal application of NO releasing drugs is effective on pre-induction cervical ripening process of the labor. It directly and through stimulation of prostaglandin and cyclooxygenase-2 (COX2), release of cytokines, and

inhabitation of thromboxane-A2 (TXA2) facilitates cervical ripening without causing complications such as fetal distress. Several clinical trials have ascertained the ability of the topical application of NO donors to promote cervical ripening, and labor induction.

Recent evidence has emerged about the role that locally applied NO donors play in cervical ripening and that NO-donors are effective and safe cervical ripening agents. A recent Cochrane Database review of the existing evidence in humans suggest that NO donors can be a useful tool in the process of induction of labor causing the cervix to be more favorable in comparison to placebo. The authors concluded that, additional data are needed to assess the true impact of NO donors on all important labor process and delivery outcomes.

We hypothesize that using a NO donor as an adjuvant to misoprostol/ intra-cervical Foley bulb for induction of labor in women with gestational hypertension and/or preeclampsia will have a synergistic effect by ripening the cervix, and shortening the overall duration of labor. If our hypothesis is confirmed, this approach may represent a significant advancement in clinical care because it will potentially significantly decrease the rate of Cesarean delivery women with gestational hypertension or preeclampsia, where the rates of surgical interventions are very high. The existing evidence also implies the NO adjuvant method will be reducing maternal blood pressures, thereby decreasing the utilization of intrapartum anti-hypertensives.

Here, we propose a randomized controlled trial (RCT) of nitric-oxide donor (NOD) isosorbide mononitrate (IMN) versus placebo as an adjuvant to misoprostol/ intra-cervical Foley bulb for induction of labor to decrease rate of cesarean deliveries in pregnancies complicated by gestational hypertension or preeclampsia (≥24/0 weeks' gestation)

The primary outcome will be rate of cesarean delivery. Secondary outcomes include interval time to delivery, acute use of anti-hypertensives and incidence of maternal/neonatal complications associated with use of IMN, to the point of discharge/transfer.

2.0 Specific Aims:

Specific aim 1: To determine if intravaginal administration of NOD isosorbide mononitrate (IMN) as an adjuvant to misoprostol/ intra-cervical Foley bulb for induction of labor decreases the rate of cesarean deliveries in pregnancies complicated by gestational hypertension or preeclampsia (≥24/0 weeks' gestation)

Specific aim 2: To determine if the use of intravaginal administration of NOD isosorbide mononitrate (IMN) as an adjuvant to misoprostol/ intra-cervical Foley bulb for induction of labor reduces the interval time to delivery.

Specific aim 3: To evaluate the safety of NOD isosorbide mononitrate (IMN) administered at the time of induction of labor in terms of frequency of intrapartum outcomes including placental abruption, need to treat with acute antihypertensive

medications, uterine hyperstimulation, maternal hypotension, atony, side effects (headache, nausea, vomiting, dizziness), and neonatal resuscitation.

3. Study Design

3.1 Primary Research Question:

Does intravaginal administration of NOD isosorbide mononitrate (IMN) as an adjuvant to misoprostol/ intra-cervical Foley bulb for induction of labor decreases the rate of cesarean deliveries in pregnancies complicated by gestational hypertension or preeclampsia?

Hypothesis 1: Compared to placebo, administration of intravaginal IMN as adjuvant to induction of labor decreases rate of cesarean deliveries in pregnancies complicated by gestational hypertension or preeclampsia.

3.2 Secondary Research Questions:

3.2.1 Does use of intravaginal NOD isosorbide mononitrate (IMN) as an adjuvant to misoprostol/ intra-cervical Foley bulb for induction of labor reduces the interval time to delivery?

Hypothesis 2: Compared to placebo, administration of intravaginal IMN at the time of induction of labor reduces the time interval from induction to vaginal delivery.

3.2.2 Is use of intravaginal IMN as an adjuvant induction agent in pregnancies complicated by preeclampsia associated with a favorable risk/benefit ratio?

Hypothesis 3: Administration of intravaginal IMN as an induction agent is safe and not associated with an increased risk of placental abruption, use of anti-hypertensives, maternal hypotension and uterine hyperstimulation, atony, meconium stained fluid compared to placebo, need for neonatal resuscitation.

3.3 Design Summary

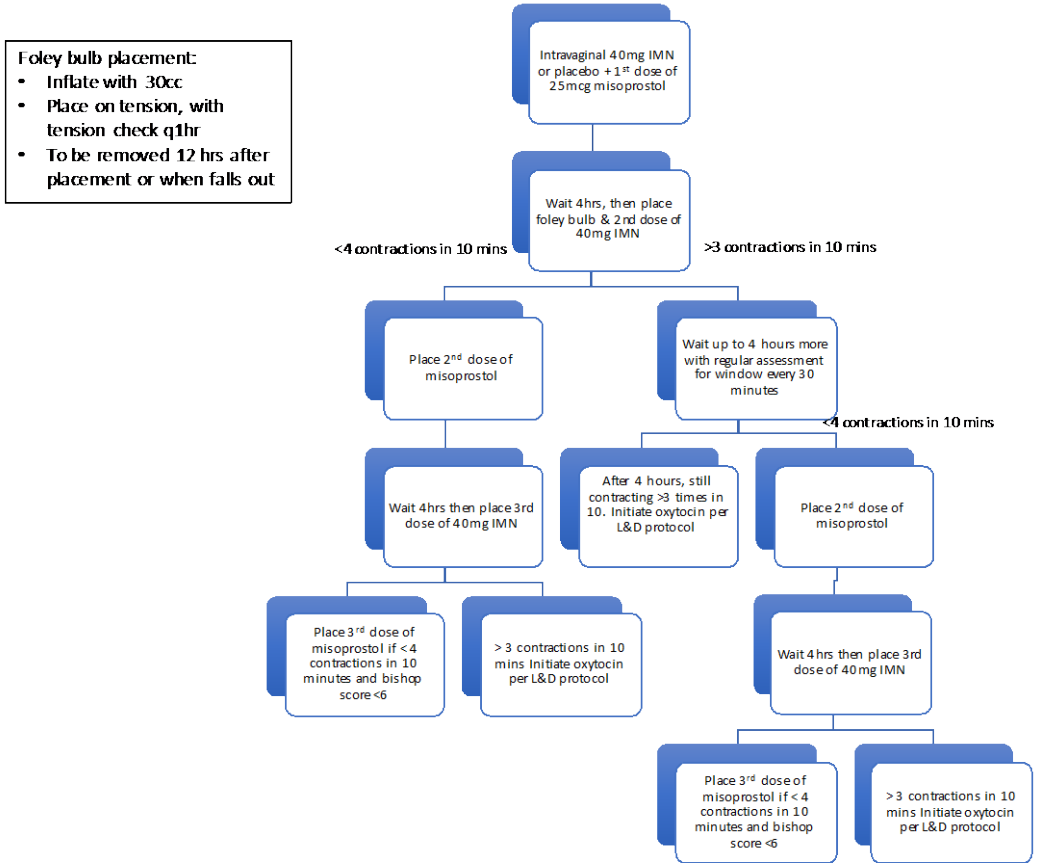
We are proposing a double blinded, placebo controlled, randomized clinical trial of patients undergoing induction of labor for gestational hypertension or preeclampsia. Once the decision to induce will be taken, mothers will be randomized to receive either intravaginal IMN (30mg) or identical appearing placebo placed every 4hrs in the posterior vaginal fornix X 3 doses. IMN or placebo will be discontinued when active labor occurs or when the physician decides to proceed with augmentation with oxytocin or AROM. Participants will be induced using our routine induction agents, Misoprostol (25 mcg every 4 hrs for maximum of 6 doses) and an intra-cervical foley bulb will be inserted with 2nd dose of IMN or placebo. See figure 1, for further details. Regarding management of labor, physician decides when to proceed with augmentation with oxytocin or AROM.

An intra-cervical foley bulb will be placed with 2nd dose of IMN (or placebo). If unable to be placed, a higher level provided must attempt placement, if sill unable to be placed the patient will be examined every 4 hours and Foley bulb placement was reattempted if Bishop's score is still 6 or less. When the Foley bulb had fallen out, further management of labor will be at the discretion of the labor team and included expectant management, amniotomy, or IV oxytocin. If indicated,

IV oxytocin will be started per standard protocol after 4 hours from the last misoprostol dose. The rest of the obstetrical care will be similar in all arms and guided by clinical guidelines.

Figure 1. Detailed algorithm of enrollment

Isosorbide mononitrate or Placebo Combined with Misoprostol and Foley Protocol



- IMN should be administered intravaginal every 4 hours for maximum of 3 doses
- Misoprostol should be administered intravaginal every 4 hours for maximum of 6 doses, if < 4 contractions in 10 minutes and bishop score <6
- If cervical Foley bulb cannot be placed at initial exam, a second higher level provider must attempt. If still unable to place, repeat exam in 1-2 hours from misoprostol placement to reattempt Foley placement.
- In order to call it a failed placement attempt, an attempt must be made with patient placed in stirrups and under direct visualization.
- Remove Foley if still in place after 12 hours from placement. Can continue with misoprostol use after Foley is removed as long as it meets criteria noted above.
- Oxytocin can be initiated 4 hours after placement of last misoprostol, regardless of whether cervical Foley still in situ

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria:

- Women older than 18 years at the time of induction of labor with the ability to give informed consent
- Induction of labor for clinical diagnosis of preeclampsia
- Unfavorable cervix (Bishop's score of less than 6) See below
- Cervical dilation 2cm or less
- Singleton
- Gestational age ≥ 24 weeks
- English speaking

3.4.1.1 Bishop Score

The Bishop Score is the most commonly used method to rate the readiness of the cervix for induction of labor. The Bishop Score gives points to 5 measurements of the pelvic examination dilation, effacement of the cervix, station of the fetus, consistency of the cervix, and position of the cervix. The link below has a calculator that examiner will use to calculate a Bishop score prior to randomization.
http://perinatology.com/calculators/Bishop%20Score%20Calculator.htm

CERVICAL EXAM	POINTS 0	1	2	3	SUBSCORE
Dilation (cm)	Closed (•)	1-2 cm ( )	3-4cm ( )	5 - 6cm ( )	0
Effacement (%)	0-30% ( )	40-50% (•)	60-70% ( )	80% ( )	1
Station	-3 ( )	-2 ( )	-1, 0 (•)	+1, +2 ( )	2
Consistency	Firm ( )	Medium (•)	Soft ( )		1
Position	Posterior ( )	Mid ( )	Anterior (•)		2
Reset			BISHOP'S SCORE		6

3.4.1.2 Gestational Age Determination

Gestational age is determined in the following manner and is denoted as "project gestational age (GA)." The "project estimated date of confinement (EDC)," which is based on the project GA, cannot be revised once a determination has been

made. Because the project EDC depends on information from the earliest dating ultrasound, if no ultrasound has been performed previously, one must be performed before the patient can be enrolled.

1. The first day of the last menstrual period (LMP) is determined and a judgment is made as to whether or not the patient has a “sure” LMP date.

2. If the LMP date is unsure, the ultrasound measurements obtained at the patient’s first ultrasound examination are used to determine the project GA by the standard method of ultrasound GA determination at that institution.

3. If the LMP date is sure and the ultrasound confirms this GA within the number of days specified in Table 3 1, then the LMP-derived GA is used to determine the project GA.

4. If the ultrasound-determined GA does not confirm the LMP-generated GA within the number of days specified in Table 3-1, then the ultrasound is used to determine the project GA.

Table 3-1. Cutoffs for Using LMP to Determine Gestational Age

Gestational age range at first ultrasound by LMP	Method of Measurement	Ultrasound agreement with LMP
≤ 8 6/7 weeks	CRL	± 5 days
9 0/7 weeks to 13 6/7 weeks	CRL	± 7 days
14 0/7 weeks to 15 6/7 weeks	BPD, HC, AC, FL	± 7 days
16 0/7 weeks to 21 6/7 weeks	BPD, HC, AC, FL	± 10 days
22 0/7 weeks to 27 6/7 weeks	BPD, HC, AC, FL	± 14 days
28 0/7 weeks and beyond	BPD, HC, AC, FL	± 21 days

3.4.2 Exclusion Criteria:

- Contraindication to vaginal delivery
- Contraindication to misoprostol
- Fetal Demise
- Major fetal anomaly
- Non-english speaking women
- HIV
- Medical conditions requiring assisted second stage
- Category III tracing
- Eclampsia
- Hemolysis Elevated Liver enzymes Low Platelets syndrome
- DIC or active hemorrhage before randomization
- Hypersensitivity to isosorbide mononitrate
- Isosorbide mononitrate should not be used in cases of acute myocardial infarction with low filling pressure, acute circulatory failure (shock, vascular collapse), or hypertrophic obstructive cardiomyopathy (HOCM), constrictive pericarditis, low cardiac filling pressures, aortic/mitral valve stenosis and diseases associated with a raised intra-cranial pressure e.g following a head trauma and including cerebral hemorrhage.
- Isosorbide mononitrate should not be used in patients with severe anemia, severe hypotension, closed angle glaucoma or severe hypovolaemia.

- Isosorbide mononitrate tablets contain lactose and therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

3.5 Study Procedures

3.5.1 Informed consent

Written informed consent must be obtained from patients before they can be randomized into the study. Full disclosure of the nature and potential risks of participating in the trial are to be made. Consent forms will be according to the requirements of the IRB and are required by the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Women who are not fluent in English will not be enrolled. A copy of the signed consent form will be provided to the patient.

3.5.2 Screening

Under the direction of the PI, trained research nurses will be available to **screen** and **consent** patients according to study protocol. We will enroll patients at the time of admission to labor and delivery (L&D) for induction of labor. All patients admitted for induction of labor for preeclampsia will be approached by the research nurses and will be provided with information and consent forms for the study so that if an emergent cesarean delivery is required in the near future the patient will already be informed about the study. Medical records of all potential patients will be reviewed and those who satisfy inclusion and exclusion criteria will be approached for informed consent. A screening and enrollment log will be used to track all patients approached for the study.

3.5.3 Randomization and Masking

After obtaining informed consent, women undergoing an induction of labor for preeclampsia will be randomized to either 30mg IMN given intravaginal with placement of misoprostol/foley bulb (as clinically indicated) or placebo in a 1:1 ratio. Randomization in each group will be by simple randomization, and will be computer generated. A confidential computer-generated simple randomization will be prepared and provided on an ongoing basis to a designated investigational pharmacist (all other study staff will be blinded). The investigational pharmacy will prepare identical appearing suppositories of IMN (30mg) or placebo according to the randomization sequence and deliver to a dedicated secure area in the labor and delivery area. A randomization log with study medication number, patient name and medical record number will be used to track the randomization process.

3.5.4 Drug Administration

When the decision is made to proceed with induction of labor for preeclampsia, and after ensuring for a consented patient, an order to give the study medication will be activated and the available study medication will be administered by the provider. The patient is considered randomized once the medication is dispensed. The investigational drug pharmacy will deliver the next study medication to the labor and delivery unit if a subsequent consented patient is already identified.

3.5.5 Baseline Procedures

- Routine intrapartum and postpartum care at each center will be provided to patients by their clinical providers who will be blinded to the study interventions.
- Trained and experienced research nurses in obstetric and perinatal outcomes abstraction at each center (also blinded to study medications) will be responsible for research data abstraction from patient medical records

Maternal and delivery outcomes will be collected during hospital stay. Occurrence of medication adverse effects or any of the pre-specified outcomes will be recorded by review of medical records by research nurses.

4. Outcome Measures

4.1 Primary Outcome: The primary outcome of the study is rate of cesarean delivery

4.2 Secondary outcomes:

a. Time to active labor (defined as dilatation 5 cm or greater),
   Delivery within 12 hours
   Delivery within 24 hours
   Maternal length of stay (defined as length of time from admission for induction to discharge postpartum, days)
   Indication for cesarean delivery
   Need to treat with acute antihypertensive medications
   Uterine hyperstimulation (either a series of single contractions lasting 2 minutes or more OR a contraction frequency of five or more in 10 minutes)
   Maternal hypotension (Symptomatic with blood pressure systolic of less than 90 millimeters of mercury (mm Hg) or diastolic of less than 60 mm Hg)

b. Maternal side-effects (headache, nausea, vomiting, dizziness, or any other unexpected adverse effect)

A composite maternal morbidity outcome is pre-specified to include one or more of the following during labor, delivery, or in the immediate postpartum during admission:

- third- or fourth-degree perineal laceration
- blood transfusion
- endometritis
- wound separation–infection (defined by the need for additional wound closure or the need for antibiotics)
- hysterectomy
- intensive care unit admission
- maternal death

Other maternal secondary outcomes analyzed will be:

- placental abruption
- chorioamnionitis (defined by the presence of maternal fever 100.4°F or greater in the presence of maternal or fetal tachycardia or fundal tenderness)
- use of terbutaline
- intrauterine pressure bulb
- amnioinfusion
- analgesia use

A composite neonatal morbidity outcome is pre-specified to include one or more of the following before neonatal discharge:

- severe respiratory distress syndrome (defined as intubation and mechanical ventilation for a minimum of 12 hours), culture proven presumed neonatal sepsis
- neonatal blood transfusion

- hypoxic–ischemic encephalopathy
- intraventricular hemorrhage grade 3 or 4
- necrotizing enterocolitis
- receipt of head cooling
- Other neonatal outcomes analyzed will be neonatal intensive care unit admission, neonatal intensive care unit admission greater than 48 hours, and neonatal length of stay (days).

5. Statistical Considerations

5.1 Sample size calculation:

Using data from our prior studies using the intended study population at The Ohio State Wexner Medical Center the incidence of gestational hypertension or preeclampsia is 10-15%.

Data abstracted from those enrolled in biorepository for gestational hypertension or preeclampsia over one year period and excluding those who were delivered for gestational hypertension or preeclampsia who had cesarean section for breech, prior cesarean section or uterine surgery, HELLP syndrome, eclampsia.

295 women underwent induction of labor for gestational hypertension or preeclampsia 48% (n=141) ended up with cesarean delivery after failed induction of labor or non-reassuring fetal well being.

Gestational Age Distribution for Gestational Hypertension or Preeclampsia Induction

Gestational Age in weeks	Number of women IOL for gHTN or PE	CS rate
24-28 wks	13	10 (77%)
28-30 wks	15	11 (73%)
30-32 wks	26	18 (69%)
32-34 wks	39	19 (49%)
34-36 wks	56	20 (34%)
36-37 wks	35	12 (34%)
37-38 wks	57	22 (38%)
38-39 wks	17	3 (18%)
39-40 wks	8	2 (25%)
40-41 wks	2	1 (50%)

Review of literature reveals is similar to OSU numbers, with the overall rate of cesarean delivery after induction of labor for gestational hypertension or preeclampsia ranges from 40% to 70%. Based on available data, we anticipate that the expected rate of the primary outcome in the women undergoing induction of labor for gestational hypertension or preeclampsia 45%. For this proposal, we will estimate a conservative relative reduction effect of 30-35%.

The table below provides the sample size calculations needed to achieve 80-90% power to detect 30-35% difference in the primary outcome between women receiving IMN or placebo at time of their induction of labor for preeclampsia, using a two-tailed alpha of 0.05.

Table 1. Total sample size required to detect a difference in primary outcome women undergoing induction of labor and receiving IMN or placebo (alpha at 0.05, variable primary outcome rates, power, and effect sizes)

Relative reduction (%)	Power (%)	Primary Outcome Rate in Placebo group				
		35%	40%	45%	50%	55%
30	90	784	644	540	462	380
	85	670	550	460	394	326
	80	586	480	404	346	284
33	90	656	540	430	368	306
	85	562	462	368	316	276
	80	490	404	322	276	242
35	90	586	482	406	330	290
	85	502	412	348	282	248
	80	438	362	304	248	216

Assuming the primary outcome to be 45 %, close to 1:1 enrollment and anticipating that no more than 2% of randomized women to be lost to follow up, a sample size of 400 women will achieve >85% power to detect a 33% relative reduction in primary outcome overall.
Given the study design and that randomization will occur once decision to proceed with induction occurs, there will be no concern for loss to follow up or missing outcome data on any women. Regarding concern for non-compliance, given study design we propose that it is unlikely that participant would not get their assigned treatment.

5.2 Interim Analysis

Interim statistical analyses of clinical trials will be at least once a year to review trial results; however, the exact timing of the interim analyses is at the discretion of the PI. A formal detailed statistical report will be written by the PI which presents the results of every aspect of the study, including all baseline variables, protocol adherence, all outcome variables, adverse events reported and center performance in terms of recruitment, data quality, loss to follow-up and protocol violations. However, the main emphasis is on the primary outcome as well as maternal safety outcomes. It is recognized that any decision to terminate the study would not be reached solely on statistical grounds but on a number of complex clinical and statistical considerations.

5.3 Unblinding Criteria

This is a double-blind study—neither the patients nor the physician/health care providers are aware of the drug allocation during the duration of the study. In the event of a SAE thought to be related to the study drug, the patient will be treated as if she has received IMN. If medical care requires unblinding of the medication, the pharmacist will unblind the patient treatment assignment and notify the PI.

5.4 Feasibility: There are 5000 deliveries per year in at The Ohio State Wexner Medical Center and approximately 8% of women are diagnosed with gestational hypertension or preeclampsia and approximately 2/3 undergo induction of labor therefore approximately 264 women per year would be eligible for enrollment. Given the high-risk nature of this population it is reasonable to anticipate a consent and randomization rate which is higher than that which is accounted for above. With only 50% consent rate, 132 women may be randomized annually. Our conservative estimate suggests that this study can be completed in approximately 3 years.

5.5 Data analysis: Analysis will be by intent-to-treat. Preliminary analyses will be conducted to test homogeneity of treatment groups for demographic data (gravidity, gestational age at randomization, race/ethnicity, BMI, number of prior cesarean) using the two-sample *t* test for continuous measurements and the Pearson chi-square test for categorical measurements. Primary and secondary outcomes will be analyzed between the two groups using univariable and multivariable analyses as needed.

6.0 Medication

6.1 Study drug: Isosorbide mononitrate is a drug used principally in the treatment of angina pectoris and acts by dilating the blood vessels so as to reduce the blood pressure. Research on extended release Isosorbide mononitrate as a cervical ripener to reduce time at hospital to birth is supportive. Isosorbide mononitrate is an active metabolite of isosorbide dinitrate and exerts qualitatively similar effects.
It reduces the workload of the heart by producing venous and arterial dilation. By reducing the end diastolic pressure and volume, isosorbide mononitrate lowers intramural pressure, hence leading to an improvement in the subendocardial blood flow. The net effect when administering isosorbide mononitrate is therefore a reduced workload for the heart and an improvement in the oxygen supply/demand balance of the myocardium.

For purpose of this study 30mg Isosorbide mononitrate suppositories and matching placebo have been compounded by an investigational pharmacy using using a commercial extended release tablets formulated into suppositories by SBH Medical and IDS an investigational pharmacy will manage the storage and dispensing. A prototype suppository was used to determine feasibility. Potency testing was preformed to get initial baseline then rechecked in 90 days, the results supported the shelf life and proof of concept (potency) on the suppositories. Per State Board of Pharmacy, Investigational Drug Service are not allowed to possess more than 7 days worth of non-patient specific compounded medication, and given our expected enrollment of approximately 5-6 patients per week, they will store 20 tablets of compounded medication/placebo. Suppositories will be refrigerated, and BUD is 30 days, protected from light and moisture.

The suppositories are manufacturer by:
SBH Medical, Ltd
Robert J. DuPont R.Ph. (rdupont@sbhmed.com)
655 Dearborn Park Lane, Worthington (OH) 43085
Phone: 614-847-6007; Fax: 614-847-6015
Web:

And will be stored at:
Investigational Drug Service
Doan Hall, Room 342
410 West 10th Avenue
Columbus, OH (43210)

6.1 Reported adverse reactions:

Headache
Tiredness
Sleep disturbances
Gastrointestinal disturbances
Hypotension
Poor appetite
Nausea

Other reactions that have been reported less frequently with isosorbide mononitrate modified release tablets include tachycardia, vomiting, diarrhea, vertigo and heartburn

6.2 Interaction with other medicinal products and other forms of interaction
The antihypertensive effect of Isosorbide mononitrate will increase when it is used concomitantly with phosphodiesterase type 5 inhibitors, which are used in erectile dysfunction. This can lead to life-threatening vascular complications. Patients treated with isosorbide mononitrate must not use phosphodiesterase type 5 inhibitors (e.g. sildenafil, tadalafil, vardenafil)
Concomitant use of drugs with an antihypertensive action, e.g. beta blockers, calcium antagonists, vasodilators (including neuroleptics and tricyclic antidepressants), alprostadil, aldesleukin, antihypertensives, diuretics, angiotensin II receptor antagonists etc. and / or alcohol can potentiate the hypotensive effect of Isosorbide mononitrate. Reports suggest that concomitant use of Isosorbide mononitrate increases the blood levels of dihydroergotamine and that the hypertensive effect is potentiated.

6.3 Mechanism of action: Like all organic nitrates, isosorbide mononitrate acts as a donor of nitric oxide (NO). NO causes a relaxation of vascular smooth muscle via the stimulation of guanylyl cyclase and the subsequent increase of intracellular cyclic guanosine monophosphate (cGMP) concentration. A cGMP-dependent protein kinase is thus stimulated, with resultant alteration of the phosphorylation of various proteins in the smooth muscle cell. This eventually leads to the dephosphorylation of the light chain of myosin and the lowering of smooth muscle tone.

6.4 Pharmacokinetic properties: Isosorbide mononitrate is rapidly absorbed and peak plasma levels are reached approximately 1 hour after oral dosing.
Following oral administration, bioavailability of Isosorbide mononitrate is 100%. It does not undergo a first-pass effect. Isosorbide mononitrate is eliminated from plasma with a half-life of approximately 5.1 hours. It is metabolised to isosorbide-5-MN-glucuronide, which has a half-life of approximately 2.5 hours. It is also excreted unchanged in the urine.

6.5 Use in pregnancy
Studies have shown no teratogenic effects with use of isosorbide mononitrate during pregnancy.

6.6 Placebo
Placebo will be an identically appearing suppository that has been outsourced by OSU pharmacy to a compounding pharmacy.

7.0 Conclusion
Overall, the quality of the available trials assessing the efficacy of intravaginal administration of NOD isosorbide mononitrate (IMN) as an adjuvant to misoprostol/ intra-cervical Foley bulb for induction of labor pregnancies complicated by gestational hypertension or preeclampsia is limited. The available data, however, point to potential benefit. Most studies report that NO donors probably help in causing the cervix to be more favorable at 12 to 24 hours after administration and some report women who received NO donors were less likely to experience uterine hyperstimulation without FHR rate changes, meconium-stained amniotic fluid, Apgar score less than seven at five minutes and analgesia requirements. Our objective is to determine whether NOD isosorbide mononitrate (IMN) as an adjuvant to induction of labor decreases rate of cesarean delivery in pregnancies complicated by gestational hypertension or preeclampsia.

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