Propranolol versus placebo for induction of labor: a double-blind randomized controlled trial
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Mount Sinai	Protocol Title:	Propranolol versus placebo for induction of labor: a double-blind randomized controlled trial
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Brief Summary of Research (250-400 words):
A randomized, prospective trial will be offered to women admitted to the labor floors at Mount Sinai Medical Center for labor induction. The study will be offered to women at >37 weeks' gestation, with a non-anomalous, singleton fetus in a cephalic presentation. Exclusion criteria include multiple gestations, known fetal anomalies, maternal cardiac or hypertensive disease, chronic beta blocker use, bronchial asthma, maternal or fetal indication for immediate delivery. There are 2 categories of eligibility for this study. The patients will be randomized to a one-time dose of IV propranolol or placebo, which will be blinded to both the research team and the patient. Induction of labor will otherwise follow standard protocol based on the preferences of the patient's primary obstetric provider. The primary objective will be time interval from induction to delivery; secondary outcomes will include mode of delivery, duration of latent versus active labor, maternal cardiovascular side effects, postpartum hemorrhage, and composite neonatal outcomes (i.e. birth weight, apgars, NICU admission). A sample size calculation with an 80% power ($\alpha = 0.05$) to detect a 20% difference in induction time to delivery will be conducted a priori. Based on the current available literature approximately 120 patients are needed in each arm to detect a 20% difference in induction to delivery time.

1) **Objectives:**
   To determine if a one-time dose of IV propranolol decreases the duration of labor during induction in nulliparous women.

2) **Background**
   Induction of labor is a common obstetric intervention, occurring in almost 25% of pregnancies in the United States. While some early studies suggested a possible increased rate of cesarean with induction of labor, more recent meta-analyses have shown that induction does not influence this rate. There are data from small randomized studies that demonstrate the effectiveness of propranolol, a non-selective beta-blocker, for induction of labor. This literature suggests a decrease in the amount of time to delivery and a possible reduction in cesarean section rates when propranolol is used in conjunction with oxytocin for induction of labor compared to oxytocin alone.

   Using this preliminary data from other centers, we are conducting a double-blind placebo-controlled randomized trial to determine if a one-time dose of intravenous propranolol decreases the duration of labor during induction in nulliparous women.

3) **Setting of the Human Research**
   Research will take place on the labor and delivery floor of Mount Sinai Medical Center.

4) **Resources Available to Conduct the Human Research**

Researchers will have access to all patients presenting to the labor and delivery floor at Mount Sinai Medical Center. There are 8000 deliveries are performed at Mount Sinai Hospital annually. Approximately 20% of these deliveries are inductions of labor. We expect there will be 1600 inductions per year. An a priori power analysis suggests we will need 120 patients in each arm (240 patients total) to achieve statistical significance.

Each research staff member involved in this study has completed all training necessary to conduct human research and the research team has years of experience in clinical research and extensive experience conducting clinical research at Mount Sinai Medical Center.

5) Study Design

a) Recruitment Methods

Eligible study participants, presenting to the labor floor for scheduled induction of labor beyond 37 weeks' gestation, will be approached for enrollment in the study by a study team member, which includes the PI, co-investigators, research coordinator, and recruiters (residents who explain the study and also consent patients). The research study will be introduced as voluntary participation with a one-time dose of medication or placebo to determine the effect on duration of labor. It will be explained that the remainder of the induction process and obstetric care will be standard and determined by the patient's primary obstetric provider. If the patient is interested in more information, the study team will review the consent and randomization process. Once a patient is consented, she will be randomly assigned to one of the 2 arms of the study; to a one-time dose of 2mg IV propranolol 30 minutes after starting the induction of labor (intervention arm) or placebo injection 30 minutes after starting the induction of labor (control group). Patients will be recruited at Mount Sinai Medical Center only.

Also, in order to disseminate information about the study to patients and physicians, study flyers will be posted in physicians' offices and on the labor floor.

b) Inclusion and Exclusion Criteria

The study will be offered to all nulliparous women undergoing induction of labor >37 weeks' gestational age with a non-anomalous, singleton cephalic presenting fetus. Exclusion criteria include multiple gestations, known fetal anomalies, maternal cardiac or hypertensive disease, chronic beta blocker use, bronchial asthma, maternal or fetal indication for immediate delivery.

c) Number of Subjects

We aim to enroll 240 patients. There are approximately 8000 deliveries at Mount Sinai Medical Center each year, and about 20% of these deliveries are performed by induction

(1600 inductions per year). Based on the local population, current literature, and using an alpha of .05 and 80% power, 120 participants are needed in each arm of this study.

d) Study Timelines

After informed consent has been obtained, the duration of the subject participation will be start of induction to hospital discharge. We expect to enroll patients over a two-year period. We will allow an additional 6 months to perform data analysis.

e) Endpoints

The primary outcome will be duration of induction to delivery. Secondary outcomes include mode of delivery, duration of latent versus active labor, maternal cardiovascular side effects, postpartum hemorrhage, composite neonatal outcomes (i.e. birth weight, Apgars, NICU admission, hypoglycemia and cardiopulmonary complications).

The induction process may be terminated in any patient at any time regardless of this study due to fetal heart rate abnormalities and in labor requiring cesarean delivery.

f) Procedures Involved in the Human Research

This study is considering if current standard induction of labor in combination with a single dose of intravenous propranolol is associated with improved outcomes including greater percentage of women delivered within or less than 24 hours. We will also assess other maternal and neonatal outcomes including cardiovascular side effects, postpartum hemorrhage, duration of latent versus active labor and cesarean delivery.

Due to the objectives of the study, the identity of test and control treatments will not be known to investigators, research staff, or patients. The following study procedures will be in place to ensure double-blind administration of study treatments. Packaging and labeling of test and control treatments will be identical to maintain the blind. The study blind will be broken on completion of the clinical study and after the study database has been locked. During the study, the blind may be broken only in emergencies when knowledge of the patient's treatment group is necessary for further patient management.

Each patient will be assigned a unique identification code. The code will be linked to the name and date of birth in an encrypted password-protected linking key code file which will be stored on the PI's personal network folder in the Hospital IT server, accessible by the PI only. The data will be stored in a separate password-protected database by the unique identification code. The database will be stored on a secure desktop at Mount Sinai hospital.

Patients will undergo standard induction of labor per their primary obstetric provider. At Mount Sinai, this is typically with the placement of a Foley balloon or vaginal misoprostol for cervical ripening, which have both been well-described in the Obstetric literature and are minimal risk interventions. Some patients will require epidural placement prior to or immediately following Foley placement. Typically, induction continues after cervical ripening with administration of IV oxytocin.

After induction is started with Foley or misoprostol placement, 30 minutes will pass before administration of the one-time study medication. There is minimal risk associated with a one-time dose of intravenous propranolol in the setting of an induction of labor. The patient may experience hypotension or bradycardia if propranolol is received, so the blinded dose administration will be 30 minutes following the onset of induction to ensure maternal hemodynamic stability, particularly if an epidural is in place. The study medication will be administered over a 2 minute IV push (per administration instructions of IV propranolol). Using intravenous propranolol for this use has been described in the Obstetric literature in randomized trials with no reported maternal or fetal adverse effects in prior studies. There is no risk from not using IV propranolol.

Administration of IV oxytocin for the purpose of induction of labor has additionally been well described in the literature. Administration of IV oxytocin is closely regulated by the labor floor staff, as too much has been associated with too frequent uterine contractions resulting in fetal distress. As the patients recruited for this study are all being induced, they will require oxytocin at some point during their induction, therefore this risk is unavoidable.

All patients receiving IV oxytocin are closely monitored with external tocometry that evaluates frequency of contractions. If a patient achieves more than 5 contractions in 10 minutes the amount being administered is decreased. This is in concordance with standard labor protocols that have previously been established for patient safety. Enrollment in this study does not place a patient at increased risk over other patients undergoing induction of labor.

Data collected will include demographic variables such as age, parity, BMI, race will be collected, as well as gestational age, bishop score, indication for induction, mode of delivery, time to full dilation, time to delivery, epidural use, and length of

ruptured membranes. Neonatal outcomes including birthweight, Apgars, hypoglycemia, cardiopulmonary complications and NICU admissions will be assessed, as well as maternal outcomes including EBL, hypotension, and bradycardia.

g) Specimen Banking

N/A

h) Data Management and Confidentiality

No specimens will be sent out or received in this trial.

All data is de-identified; patients are followed by subject number. Identifiable patient information (consent forms & consent documentation) are kept separately from any data collected. All data is stored in a locked cabinet. Identifiable enrollment statistics are kept in a password-protected computer spreadsheet that is only accessible by members of the research team on a departmental J Drive.

Data will be analyzed on an intention to treat basis. Statistical analysis will be performed by SAS using X^2 test or Fisher exact test (for categorical variables) and student T-test or Mann-Whitney U test (for continuous variables). Statistical significance will be set at $p<0.05$.

i) Provisions to Monitor the Data to Ensure the Safety of Subjects

Part I: Elements of a Data and Safety Monitoring Plan
MSSM Principal Monitor:
The principal monitor for this study is the PI:
Last Name: Stone
First Name: Joanne
Academic Title: Professor
Department: OB/GYN – Maternal Fetal Medicine
Mailing Address: [redacted]
Phone: 212-241-0535
Fax: 212-348-7438
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Dr. Stone has years of experience in research and clinical practice and is qualified to serve as the principal monitor to ensure the safety of participants. All adverse events, subject compliance with the protocol, drop outs, and all study data will be closely monitored and reviewed on an annual basis.

Standard of care and labor floor protocol will be followed.

If there is a temporary or permanent suspension of the study, in addition to the PPHS, the FDA and clinicaltrials.org will be notified.

j) Withdrawal of Subjects

There are no anticipated circumstances under which subjects will be withdrawn from the research without their consent.

6) Risks to Subjects

The use of propranolol in pregnancy has been studied in both animal models and humans. While chronic beta blocker use carries some fetal risk of intrauterine growth restriction and preterm birth, along with neonatal hypoglycemia, this is not likely with a one-time dose in a patient who is naive to this medication class. In vitro studies of propranolol on placental vasculature demonstrate a very minimal risk of placental vasospasm and decreased blood flow - propranolol is more likely to cause placental vascular relaxation. There is a risk of maternal hypotension or bradycardia following administration of propranolol but this is low risk due to the non-selective nature of the beta-adrenergic blockade and minimal effect propranolol has on the autonomic nervous system. Overall these risks are considered low for this study which utilizes a one-time dose of the medication with a slow IV push. IV propranolol has been used in multiple studies of pregnant women in active labor or for induction without adverse maternal or neonatal effects documented (Pergialiotis et al, Arch Gynecol Obstet 2016 – Table 1).

The patients in our study are all scheduled for induction of labor, where a transcervical Foley catheter has been chosen as the method of cervical ripening by the patient's physician. The inherent nature of induction requires intervention that initiates contractions. Contractions are painful for most women; therefore all women in this study will have access to labor analgesia as requested by the patient. In addition, enrollment in this study will not alter the current strategies regarding labor analgesia or induction protocols with the exception of an additional injection of study medication.

The risk of placement of the transcervical Foley catheter of this is minimal. All patients in this study will be receiving this transcervical Foley catheter which is easily removed at any point. However, the purpose of this apparatus is to dilate the cervix and is therefore removed once extruded by the cervix.

IV oxytocin is a closely monitored medication by both nursing staff and physician staff. There is a strict protocol in place in regards to the amount, timing, and frequency of administration. The medication once given is rapidly cleared from the body.

There is always the risk of loss of confidentiality; however, there are procedures in place to minimize this risk. To ensure confidentiality, the following system will be adhered to: When subjects are enrolled in this study, they will be assigned a unique identification code. Corresponding medical record numbers for each code (keycode) will be stored in a password locked document on the MFM server that can be accessed only by members of the research team. At the conclusion of the data extraction, the outcome variable will be assessed and the key codes to the medical record numbers will no longer be necessary and that information will be permanently erased from the keycode file. Electronic data with identifiers will be encrypted according to Data Security Standards.

7) Provisions for Research Related Harm/Injury

The patients will receive standard obstetric care and have access to the obstetric staff (physicians, nursing) as well as all of the resources on the labor floor including the use of the ORs, blood bank, continuous fetal monitoring. Any potential adverse events are inherent to the induction process itself and regardless of the study.

8) Potential Benefits to Subjects

Direct benefit to subject is unknown. However, the potential benefit is that we may find that using propranolol at the start of induction may reduce the amount of time to achieve delivery, which may result in a lower risk of bleeding and/or infection. We may find that it affects the mode of delivery such that the prevalence of cesarean delivery is reduced.

9) Provisions to Protect the Privacy Interests of Subjects

The patients will be approached by the physicians on the labor floor to determine if they are willing to be included for randomization. Their participation will not require any additional examinations. They will only be approached once by the physician on the labor floor to determine if they are willing to participate. All research-related discussions will be held in the patient's private room. Any questions will be answered and fully discussed to maximize patient comfort. If they chose to participate they will be randomized and receive care within the accepted standards.

10) Economic Impact on Subjects

There are no foreseeable costs that subjects may incur through participation in the research.

11) Payments to Subjects

There will be no payment to subjects.

12) Consent Process

The patient will be consented after admission to the labor floor and informed consent will be obtained in the patient's private room. All study participants must be English speaking, as

resources to translate the consent in other languages are not available. We will be following SOP HRP-090 Informed Consent Process for Research.

13) Process to Document Consent in Writing

Consent will be documented in writing on the form. A copy of the signed informed consent will be placed in the patient's chart along with a brief progress note indicating study enrollment with a brief discussion of the consent process.

14) Vulnerable Populations

Include	Exclude	Vulnerable Population Type
	X	Adults unable to consent
	X	Individuals who are not yet adults (e.g. infants, children, teenagers)
	X	Wards of the State (e.g. foster children)
X		Pregnant women
	X	Prisoners

15) Multi-Site Human Research (Coordinating Center)

N/A

16) Community-Based Participatory Research

N/A

17) Sharing of Results with Subjects

N/A

18) External IRB Review History

N/A

19) Control of Drugs, Biologics, or Devices

This study will use generic propranolol hydrochloride injectable as the study drug. This drug meets requirements for IND exemption. The study team is in the process of applying to the Food and Drug Administration for an IND exemption for this study.

The study drug (propranolol hydrochloride, USP) and placebo will be dispensed, stored, labelled and randomized by the Mount Sinai research pharmacy (IDS). An order set will be created to dispense the study drug according to the randomization protocol after the patient has consented to randomization. There is no compounding required.