Propranolol Rescue of Prolonged Labor (PROPEL)

A randomized, double-blind, placebo-controlled multicenter investigation of propranolol's effect on cesarean delivery rate among women with prolonged labor

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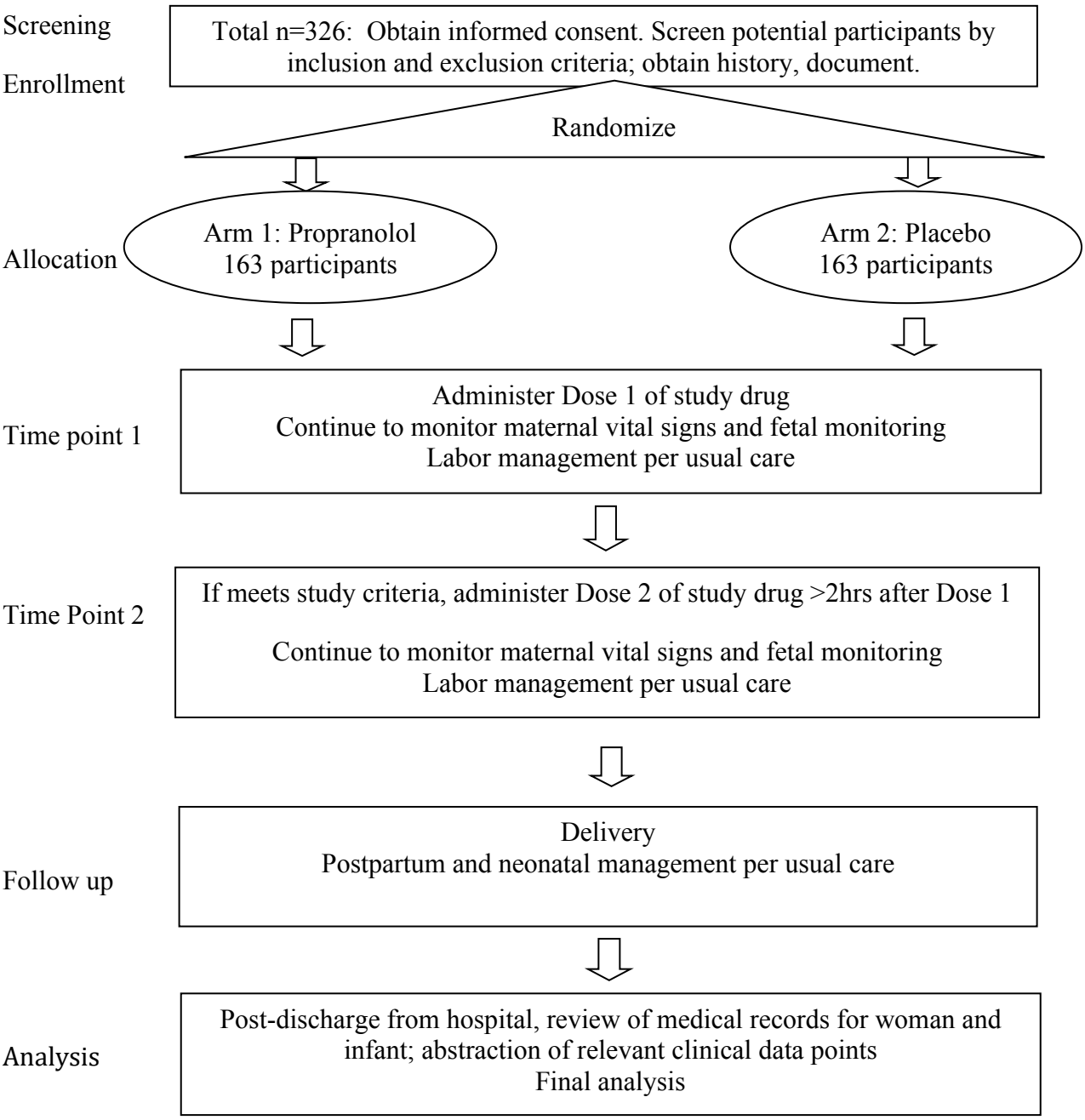
Study Drug/Study Device: Propranolol hydrochloride

LIST OF ABBREVIATIONS

AE	**Adverse event**
DSMB	**Data safety monitoring board**
CD	**Cesarean delivery**
EFM	**Electronic fetal monitoring**
GBS	**Group B streptococcus**
HIE	**Hypoxic ischemic encephalopathy**
ICN	**Intensive care nursery**
ICU	**Intensive care unit**
IDS	**Investigational drug service**
IOL	**Induction of labor**
IRB	**Investigational review board**
IV	**Intravenous**
IVH	**Intraventricular hemorrhage**
NEC	**Necrotizing enterocolitis**
OB	**Obstetric**
RDS	**Respiratory distress syndrome**
SAE	**Serious adverse event**
VTE	**Venous thromboembolism**

STUDY SCHEMA



Study Summary

Title	**P**ropranolol **r**escue **o**f **p**rolonged **l**abor
Short Title	**PROPEL**
Methodology	Double-blind randomized controlled trial
Study duration	24 Months
Study Center (s)	Multi-center: Hospital of the University of Pennsylvania and Pennsylvania Hospital
Objective	To compare cesarean delivery (CD) rates in women given IV propranolol versus placebo for treatment of prolonged labor.
Number of Subjects	326
Diagnosis and Main Inclusion Criteria	Meets criteria for prolonged labor: 1. cervical dilation <6 cm after ≥12 hours with ruptured membranes and receiving oxytocin OR 2. cervical dilation >6 cm and <1 cm dilation change over ≥2 hours with ruptured membranes and receiving oxytocin AND ≥16 years old, ≥ 36 weeks gestation; Singleton gestation in vertex presentation; non anomalous fetus
Study Product (s), Dose, Route, Regimen	IV Propranolol – 2mg; one possible repeat dose ≥2 hours later Normal saline placebo- 2 mL; one possible repeat dose ≥2 hours later
Duration of administration	Eligible for maximum of one repeat dose ≥2 hours after first until reaches 10cm dilation
Primary Outcome	Cesarean delivery
Statistical methodology	Intention to treat analysis, chi-square test for categorical variables, two-sample t-test for continuous variables

1 BACKGROUND AND RATIONALE

1.1 Condition Background

Since the 1980's, the rate of cesarean delivery (CD) in the US has climbed dramatically to its current rate around 33% of all deliveries.[1] While CD can be a life-saving procedure for both mother and baby, it also carries significant risks, both immediate and in future pregnancies. Currently, 34% of all CDs performed in the United States are for labor arrest, making labor arrest the most common indication for primary cesarean delivery.[1] The etiology of labor arrest is thought to be related to 3 primary factors – contraction strength or frequency, the size and position of the fetus, and the shape and space in the pelvis. Of these three etiologies, the most common cause of protracted labor is inadequate contraction strength and/or frequency. Additionally, this is the only truly modifiable etiology of labor arrest, so it is an important target for therapeutic intervention. Current standards for clinical management of labor arrest included artificial rupture of membranes and administering oxytocin to increase contraction strength and frequency. Even with these interventions, attempts to resolve labor arrest still often fail, up to 50% of the time.[1] There is a great clinical need for additional strategies to treat labor arrest and reduce the associated rates of CD and maternal morbidity. While some small prior studies have identified treatment with propranolol to have possible benefit in management of labor dystocia, others have not found the same results, likely due to heterogeneous populations being evaluated. Propranolol warrants further study to evaluate its effectiveness as an intervention for treatment of labor arrest.

1.2 Study Agent(s)/Devices Background and Associated Known Toxicities

Propranolol is a nonselective β-adrenergic receptor blocking agent that specifically competes with β-adrenergic receptor stimulating agents for available receptor sites, thereby decreasing chronotropic, inotropic, and vasodilator responses to β-adrenergic stimulation. β1 adrenergic receptors are found primarily in the heart, where blockade of cardiac β-adrenergic receptors leads to a decrease in the activity of pacemaker cells and a decrease in A-V nodal conduction velocity. These actions lead to antiarrhythmic activity and control of ventricular rate. β2 adrenergic receptors are found predominantly in smooth muscle, including vascular, bronchial, gastrointestinal, and uterine smooth muscle, where blockade of these receptors results in smooth muscle constriction.

Propranolol is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma; and 4) in patients with known hypersensitivity to propranolol hydrochloride. Adverse events reported with use of propranolol include bradycardia, hypotension, congestive heart failure, heart block, cardiac arrest, dyspnea, and cutaneous ulcers.

Early in vitro studies in the 1960's identified the presence of β receptors on the human uterus. In 1966, the first clinical studies demonstrated that administering IV propranolol to pregnant women at term caused increased contraction strength and frequency.[2] In 1996, the first clinical trial attempting to utilize propranolol as a labor augmentation agent was published. In this study, the authors demonstrated a nearly 50% reduction in the rate of CD among women with labor dystocia who were given IV propranolol compared to women with labor dystocia given placebo.[3] Subsequently, there have been 5 additional studies examining propranolol as labor medication.[4-8] One non-blinded RCT administered 2mg

of IV propranolol to nulliparous women admitted for labor or for induction of labor (IOL).[8] Notably, these patients did not have any diagnosis of dystocia, and the medication was given as an adjunct to normal labor management. The CD rate was quite low overall in this study, and there was no significant difference between the two groups. Another study was a double-bind RCT of women with arrest of dilation, with an unchanged cervical exam for 2 hrs anywhere from 2-7cm during labor.[7] Patients received 2mg IV propranolol with a repeat dose in 1 hr if unchanged, vs placebo. This study also had a low overall CD rate, with no difference between groups. Two additional studies have evaluated the use of propranolol as an induction agent.[4,6] Both were done in Iran where the induction protocol is quite different than in the US. The first study, which included only nulliparous patients, showed no difference in CD rate but a 2.5 hour shorter time to delivery; the second study found a significant difference in CD rate from 40 to 20% in the PO propranolol group. Finally, one additional study evaluated the administration of propranolol to women with arrest of active phase but with a low rate of oxytocin usage – 28% of propranolol the group versus 60% of placebo group.[5] Ultimately this study showed no difference in the CD rate, but given the low use of oxytocin in this study, it is less applicable to most obstetric practice. In the 7 total published clinical trials referenced above, there were no reported safety issues, side effects, or incidences of worse maternal or neonatal outcomes in those patients who received propranolol. Each of the 7 trials demonstrated the safety of administering this medication in labor.

The dose regimen in our proposal (2mg IV followed by up to one repeat dose ≥2 hours later) is based on previous clinical trials of propranolol used in labor, as well as current accepted practice and propranolol dosing regimens used in other clinical scenarios. We believe that IV is more appropriate than PO in this context as the onset of action and half-life of the IV formulation is shorter than PO and more appropriate for the time frame of intended effect. According to the propranolol package insert, the usual dose is 1 to 3 mg, and the rate of administration should not exceed 1 mg per minute to diminish the possibility of lowering blood pressure. According to the labeling, a second dose may be given after two minutes. Our proposed protocol will be compliant with this recommendation.

1.3 Rationale

There is biologic plausibility for the role of propranolol in labor management. Prior studies have suggested possible benefit, but they have been small and heterogeneous with mixed results. The utility of propranolol in management of prolonged labor has not been established. This medication warrants further study to evaluate its effectiveness as an intervention for treatment of labor arrest.

2 STUDY AIMS

2.1 AIM 1: To compare CD rates among women given IV propranolol versus placebo for treatment of prolonged labor.

2.2 Endpoints

2.2.1 Primary Endpoint

- Mode of delivery (cesarean versus vaginal)

2.2.2 Secondary Endpoints

- Time (hours) from start of labor/IOL to delivery

- Time (hours) from study drug administration to delivery
- Time (hours) from start of second stage of labor to delivery
- Indication for CD
- Operative vaginal delivery
- Cumulative and maximum dose of intrapartum oxytocin received
- Postpartum hemorrhage
- Maternal blood transfusion
- Endometritis
- Chorioamnionitis
- Wound infection
- Other composite maternal morbidity: VTE, Hysterectomy, ICU admission, Maternal readmission within 7 days and 4 weeks, Maternal death
- ICN adm > 48 hours
- Composite neonatal outcome:, neonatal blood transfusion, HIE, IVH grade 3 or 4, head cooling, severe RDS, NEC, Sepsis, Death

3 PATIENT ELIGIBILTY

Subjects must meet all of the inclusion and exclusion criteria to be enrolled to the study. Study treatment may not begin until a subject is consented and randomized.

3.1 Inclusion Criteria

English-speaking

≥ 16 years of age

≥ 36 weeks gestation

Singleton pregnancy

Vertex presentation

No contraindication to a vaginal delivery

Meets at least one study criteria for prolonged labor:

1. cervical dilation <6 cm after ≥12 hours with ruptured membranes and receiving oxytocin

OR

2. cervical dilation >6 cm and <1 cm dilation change over ≥2 hours with ruptured membranes and receiving oxytocin

3.2 Exclusion Criteria

Severe preeclampsia: as patients will be receiving magnesium and possibly labetalol for hypertension control

Receiving other beta blocker

Maternal heart rate < 70 beats per minute, systolic blood pressure <90 mmHg, or diastolic blood pressure <50 mmHg on two sets of vital signs in the 1 hour prior to study drug administration: given that bradycardia and hypotension are possible side effects of propranolol

History of any form of asthma: as this is a contraindication to beta blocker use

Diabetes requiring insulin in labor: given the potential risk of neonatal hypoglycemia in the neonate

Any cardiac condition for which β blockade is contraindicated (cardiogenic shock, sinus bradycardia, and greater than first degree heart block)

Known hypersensitivity to propranolol

Intrauterine fetal demise since different labor protocols are used in these women

Major fetal congenital anomaly since rate of cesarean may be inherently different in these women, unrelated to labor

3.3 Vulnerable patient populations

Pregnant women are considered a vulnerable population. As the condition of interest is a pregnancy-related and specific condition, it is unavoidable to exclude pregnant women from this research study. However, propranolol is currently used in clinical practice in pregnant women for other medical indications, so the risks to this population are minimally increased from that experienced in routine clinical care.

Furthermore, neonates are considered a vulnerable population. We will be collecting data on neonates for our composite neonatal outcome. All risks to this vulnerable population will be minimal risk. Propranolol is a medication that is used clinically in the neonatal population for management of retinopathy of prematurity and hemangiomas. Neonatal risks of this study include the risk of neonatal hypoglycemia, respiratory depression, and bradycardia. Neonatal blood glucose screening is routine at HUP for all neonates whose mothers receive a β blocker intrapartum. Neonatal hypoglycemia is a rare but known side effect of intrapartum β blocker use. This occurs most commonly for women who receive labetalol intrapartum for blood pressure control. In one large study of over 2 million neonates, the rate of neonatal hypoglycemia was found to be 4.3% among those exposed to intrapartum β blockers, compared to 1.2% among controls. After adjusting for confounders, the odds ratio of neonatal hypoglycemia was found to be 1.68 [95% CI 1.50-1.89].[9] National guidelines do not specify maternal use of β blockers as an indication for routine blood glucose monitoring in asymptomatic infants, but this is standard of care at UPHS, so all neonates included in this study will undergo routine hypoglycemia via heel stick at 3 time points within the first 24 hours of life. There are many risk factors for neonatal hypoglycemia and it is possible that these neonates would have required a glucose check regardless of enrolling in the study. In general, approximately 30% of all neonates born at term at UPHS meet criteria for glucose screening. The only additional risks to the neonate include chart review after delivery. Subjects will be made aware of these risks and that we will be collecting information on their neonates within the consent form.

3.4 Ensuring Necessary Medical Interventions

Enrollment in this study will not alter any aspects of routine labor management. Continuous EFM and tocometry will occur on all patients in labor, consistent with standard of care. The remainder of clinical care in labor will be at the covering OB providers' discretion. The frequency and timing of cervical examinations will occur per provider discretion. Standard treatment for GBS positive and GBS unknown patients will occur. The use of internal fetal monitoring and intrauterine pressure catheter will be at the discretion of the OB provider. Standard obstetric indications for cesarean delivery will be also be at the discretion of the OB provider. There will be no additional blood draws or cervical examinations for women enrolled in this study.

3.5 Potential Benefit to Participants

The potential benefit will be reduced risk of CD among individuals randomized to the intervention arm. This will lead to a possible reduction in maternal and neonatal morbidity associated with unscheduled CD. Additionally, the results of this study will benefit future patients in labor. All efforts will be taken to minimize the risks associated with this study and the risks overall are considered minimal; therefore, the risk to subjects is reasonable compared to the benefit to patients and to society in general.

4 TREATMENT ARMS

4.1 Treatment Dosage and Administration

- Propranolol hydrochloride 2mg IV
  - One possible repeat dose of 2mg IV given ≥2 hours later if <2 cm cervical dilation change over >2 hours on subsequent exam
- Placebo – 2mL of 1% normal saline solution IV
  - One possible repeat dose of 2mL IV given ≥2 hours later if <2 cm cervical dilation change over >2 hours on subsequent exam

4.2 Toxicities

Any patient who receives treatment will be evaluated for toxicity. Each patient will be assessed for the development of toxicity according to vital sign monitoring or symptoms. In the event of developing bradycardia, hypotension, heart block, cardiogenic shock, bronchospasm, anaphylaxis, or signs of an allergic reaction, the second dose will not be administered.

4.3 Concomitant Medications/Treatments

All participants will be already receiving oxytocin for labor augmentation prior to receiving the study medication. No additional labor augmentation agents will be utilized. No additional β-blocker, antihypertensive, or vasoactive medications will be utilized in conjunction with the study medication.

4.4 Duration of Therapy

All participants are eligible for a maximum of one repeat dose of the study medication, until they reach 10cm dilation or decision is made to proceed with cesarean delivery, whichever comes first. After this point, they will not be eligible for any further study medication.

4.5 Duration of Follow Up

Women/neonate dyads will be followed for the development of any maternal or neonatal complications through the duration of the postpartum hospital stay as well as for readmissions within 30 days of delivery.

4.6 Removal of patients from protocol therapy

Patients will be removed from therapy when any of the criteria listed in Section 4.2 and 5.5 apply. The Principal Investigator will be notified and document the reason for study removal

and the date the patient was removed in the Case Report Form. The patient will be followed-up per protocol.

4.7 Blinding

This is a double blind study and therefore physicians, staff, and patients will be blinded to the patient's allocated treatment group. In the event of a potential suspected unexpected serious adverse reaction, unblinding will be undertaken by the PI. Unblinding may also be performed at the request of a senior clinician responsible for the care of a trial participant but such requests are likely to occur only in the case of an adverse clinical event and are expected to be rare. Any request to unblind treatment allocation for clinical reasons will be made directly to IDS and the treatment allocation will be reported to the relevant clinician. The PI and main trial manager will be kept informed of all instances of unblinding but remain blind to treatment allocations themselves wherever possible. All requests for unblinding will be recorded by research staff and IDS.

5 STUDY PROCEDURES

5.1 Screening for Recruitment and Recruitment Process

Women meeting the criteria listed in section 3.1 will be invited to participate in the study and written informed consent will be obtained from those who choose to participate. The screening procedures include:

- Informed Consent
- Medical history: Complete medical and surgical history
- Demographics: Age, gender, race, ethnicity
- Review subject eligibility criteria
- Review previous and concomitant medications
- Physical exam including vital signs, height and weight
- Vital signs (temperature, pulse, respirations, blood pressure), height, weight
- Adverse event assessment: Baseline adverse events will be assessed. See section 6 for Adverse Event monitoring and reporting.

5.2 Randomization

Eligible, consented women will receive pre-randomized study medication. Study medications will be prepared and randomized by the Investigational Drug Service (IDS) via a random generated randomization scheme. The randomization scheme will be generated by a pharmacy associate within IDS not involved in the clinical care of the patient. Two single-use vials of the same medication – either propranolol or placebo- will be included in a numbered bag. One vial will be used for the first dose. If a patient meets eligibility criteria to receive a repeat dose, the second vial in the same bag will be used.

5.3 Procedures During Treatment

After study enrollment, the covering clinician will place an EPIC order for "investigational study drug" and will retrieve the next available pre-randomized study medication bag that will be available in the labor floor medication room. The number labeling the study medication bag will be recorded by the clinician and the patient's identification label will be applied to the used vial of study medication after administration and returned to IDS for confirmation and record keeping. The time of administration of the study drug will be recorded by the patient's nurse in EPIC. For a repeat dose of medication, the RN will use the second vial of medication

included in the same study medication packet, record the administration of the dose in EPIC, and label and return the medication to IDS in the same manner.

Patients in both groups will undergo similar vital sign monitoring before and after each dose of study medication. Patients will have routine vital sign monitoring every 15-30 minutes depending on the stage of labor (including heart rate, blood pressure, and oxygen saturation assessment) through the duration of their enrollment in the study.

The remainder of clinical care in labor and delivery will occur as per primary OB provider's discretion as described in section 3.4.

5.4 Follow-up Procedures

During the postpartum hospital stay, women will continue to receive routine postpartum care at the discretion of their providers.

5.5 Removal of Subjects from Study

Patients can be taken off the study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted);
- Patient withdraws consent (termination of treatment and follow-up);
- Patient is unable to comply with protocol requirements;
- Patient experiences toxicity that makes continuation in the protocol unsafe;
- Treating physician judges continuation on the study would not be in the patient's best interest.
- The study is stopped.

5.6 Protections Against Physical Risk

There is minimal risk to the use of propranolol during labor. This medication is currently employed in clinical use in pregnant women, and other β-blocking medications such as labetalol are commonly used in laboring women in the University of Pennsylvania Health System. A DSMB comprised of individuals who are not investigators on the trial will be utilized to monitor for adverse outcomes. A list of mandatory events that should be reported to the DSMB within 24 hours of occurrence will be supplied to all clinicians and research coordinators managing trial patients. Also all serious adverse events will be recorded and reported to the institutional review board.

5.7 Protection against Loss of Privacy/Breach of Confidentiality

In order to protect a potential subject's privacy, study staff will only approach potential subjects in a private setting. Once consented, we will take multiple steps to protect the study subject from breach of confidentiality. The list linking the subject's name and medical record number will be kept behind the hospital firewall in a password-protected file. This file is only accessible through the hospital server to those individuals given password approval to access the file. Furthermore, the electronic database (REDCap) will be coded with a unique study identifier rather than with any individually identifiable private information. No PHI will be shared with anyone outside the institution.

6 ADVERSE EVENTS

6.1 Adverse Event Monitoring

Adverse event data collection and reporting will be done to ensure the safety of subjects who will be enrolled in the study. Adverse events will be reported in a routine manner at scheduled times during the trial. Additionally, certain adverse events will be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug/device, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

6.2 Definitions

6.2.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

For the purposes of this study, the following will be considered and adverse event:

- Maternal bradycardia < 50 beats per minute within 30 minutes of drug administration
- Maternal hypotension <80/40 mmHg within 30 minutes of drug administration
- Maternal bronchospasm
- Maternal hypoglycemia requiring treatment
- Maternal allergic reaction
- Chorioamnionitis
- Endometritis
- VTE
- Blood transfusion
- Readmission within 7 days
- NICU admission > 48 hours

6.2.2 Severity of Adverse Events

The severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

Life-threatening (grade 4): the patient was at risk of death at the time of the event.

Fatal (grade 5): the event caused death.

6.2.3 Serious Adverse Events

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

Results in death.

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

Is life-threatening (i.e. the patient was at risk of death at the time of the event).

Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

Results in persistent or significant disability or incapacity.

Is an important medical event. Essentially, any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event.

For the purposes of this study, the adverse events that would meet any of these criteria are listed below and will be documented and reported as a SAE. In addition, any unexpected event which the PI believes to have been cause or contributed to by the intervention, regardless of whether it resulted in hospitalization, will also be considered an AE or SAE.

Maternal SAE:

- Maternal death
- ICU admission
- Anaphylaxis
- Hysterectomy

Neonatal SAE:

- Death
- Blood transfusion
- Hypoxic-ischemic encephalopathy (if NICU documents HIE as diagnosis)
- Intraventricular hemorrhage Grade 3 or 4
- Severe respiratory distress (intubation and mechanical ventilation for a minimum of 12 hours)
- Necrotizing enterocolitis or rule out NEC (if NICU documents this)
- Culture proven neonatal sepsis

6.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event

Step 2: Grade the adverse event

Step 3: Determine whether the adverse event is related to the protocol therapy

Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Step 4: Determine the prior experience of the adverse event.

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

6.4 Reporting Requirements for Adverse Events

6.4.1 Expedited Reporting

- The Principal Investigator will be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- The University of Pennsylvania IRB must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR/UPIRSO).

  The following events meet the definition of UPR:

  1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
  2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
  3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.

4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

6.4.2 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

6.5 Stopping Rules

This study does not have a primary safety endpoint or place study subjects at high risk.

7 DRUG/DEVICE INFORMATION

7.1 Propranolol hydrochloride

- Other names for the drug: Inderal
- Classification - type of agent: β-blocker, antiarrhythmic
- Mode of action: Propranolol is a nonselective beta-adrenergic receptor blocking agent that specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites, thereby decreasing chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation.
- Protocol dose: 2mg IV; one possible repeat dose ≥2 hours later
- Route of administration for this study: IV push
- Incompatibilities: there are no medications that are contraindicated for use with propranolol
- Availability: commercially available, on formulary
- Side effects: hypotension, congestive heart failure, bradycardia, heart block, cardiac arrest, bronchospasm, and cutaneous ulcers. (Please refer to the manufacturer's package insert for a complete list of adverse events)
- Nursing implications: Propranolol is excreted in breast milk.

7.2 Product Preparation/Packaging, Receipt and Storage

Investigational Drug Service (IDS) of the University of Pennsylvania will purchase commercial propranolol hydrochloride 2mg/mL vials. An internal lot number and use-by date will be assigned. Visually-matching placebo vials of normal saline 0.9% will be purchased by IDS. An internal lot number and use-by date will be assigned.

IDS will dispense pre-randomized and numbered packets of study medication containing two doses of either propranolol or placebo medication. IDS will package and deliver the drugs to the locked labor floor medication room. Drug accountability will be maintained by IDS and study coordinators.

Study medication and placebo will be stored at room temperature in the locked medication room on the labor floor only accessible by floor and research staff.

8 STUDY DESIGN/STUDY ENDPOINTS

This will be a prospective, double-bling, placebo-controlled, randomized, multi-center study on the effect of propranolol versus placebo on the rate of cesarean delivery for women with prolonged labor. Please refer to section 2.3 for endpoints.

Regarding stopping rules for safety or efficacy, we do not anticipate early termination of the study for either. Issues that would be of concern would be persistent bradycardia or hypotension with therapy and unexpected events. Other findings that could trigger a safety review include the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs, or increased frequency of events.

8.1 Sample Size and Accrual

The sample size is based on the expected CD rate for women experiencing prolonged labor of approximately 45%. For a power of 80% and an alpha of 0.05, 326 women would be needed to find a decrease in rate of CD to 30%.

We estimate 40 eligible women deliver at HUP per month. We anticipate approaching 80% of these women or approximately 32 per month. With an estimated 50% consent rate, we would enroll approximately 16 women per month. Therefore, we would need 24 months to reach our target enrollment of 326 women.

8.2 Data Analyses Plans

Measures of relative risk will include 95% confidence intervals. Descriptive statistics will be presented as mean with standard deviation, median with interquartile range, or proportion with 95% confidence interval based on data type and distribution. Comparisons between groups will be performed using a Chi-square or Fisher's exact test for categorical variables and parametric or non-parametric tests for continuous variables, as appropriate. Intention-to-treat analyses will be conducted such that all patients with available follow-up measures will be included in the analysis. Statistical analyses were conducted in STATA, version 15.1 (College Station, Texas). Two-tailed P values of <0.05 will be considered statistically significant.

9 STUDY MANAGEMENT

9.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the PI and the IRB. All investigators will follow the University's conflict of interest policy.

9.2 Collection of data

We will record data on each patient regarding their demographics, obstetrical and medical history, labor and delivery admission through postpartum discharge. We will also collect neonatal outcomes on their infants through hospital discharge.

9.2.1 Private information

Only the study staff listed on the protocol approved by the Institutional Review Board will have access to individually identifiable private information about human subjects. The only individually identifiable private information about human subjects that will be collected for research purposes is the subject's name and medical record number for the purpose of linking the subject to their unique study identifier.

9.2.2 Data Protection

The individually identifiable private information that will be collected is name and medical record number for the purposes on linking the subject to their unique study number for chart review. The file linking the study number to the name, medical record number and phone number will be kept in a password-protected file on a secure server. Data will be collected primarily by the research team. The electronic database (REDCap) will be stored behind the institution's firewall in a password-protected file.

9.3 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form. Patients will not be approached for consent if clinical judgement deems them to be in an unclear state of mind (e.g. either due to excessive pain or from intravenous pain medication use).

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.4 Data Management and Monitoring/Auditing

9.4.1 Data Safety and Monitoring Plan

Safety monitoring will be performed periodically by the principal investigator. This will include assessment of accuracy of data recording, assuring de-identification of data, and that there is appropriate locked storage of data material. There will be no planned interim analyses. An advisory board will be created for continual oversight of the project. It will be comprised of faculty members within the department with extensive experience in prospective clinical trials. They will perform periodic reviews of safety data from this study. The DSMB that will be created is attached.

9.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.5.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, a IRB modification form must be completed within five (5) business days of making the change.

9.5.2 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, the ensuing guidelines will be followed:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Study personnel should report violations within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

9.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In all other cases,

study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10 References

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