Combination Oxytocin/Foley versus Oxytocin Alone for Induction of Labor in Patients with Preterm Prelabor Rupture of Membranes

Protocol

Version IV

07/02/2025

1. Introduction

1.1 Study Abstract:

Data on the optimal mode of labor induction after preterm prelabor rupture of membranes (PPROM) is lacking. Studies have shown no difference between oxytocin and misoprostol use for labor induction in this cohort (1). The preponderance of evidence from term pregnancies suggests that Foley catheter coupled with oxytocin is better than oxytocin alone, with a higher rate of delivery within 24 hours when a Foley catheter followed by oxytocin is compared to oxytocin alone. However, the use of a Foley catheter has not been evaluated in prospective studies on patients with PPROM.

1.2 Study Hypothesis:

Combination Oxytocin/Foley results in a shorter time to vaginal delivery compared to Oxytocin alone in patients with PPROM and a cervical dilation </=2cm.

1.3 Purpose of the Study Protocol

This protocol describes the background, design and organization of the randomized clinical trial. Institutional Review Board (IRB) approval will be obtained prior to beginning recruitment.

2. Background

2.1 Introduction

Data on the optimal mode of labor induction after preterm prelabor rupture of membranes (PPROM) is lacking. Studies have shown no difference between oxytocin and misoprostol use for labor induction in this cohort (1). The preponderance of evidence from term pregnancies suggests that Foley catheter coupled with oxytocin is better than oxytocin alone, with a higher rate of delivery within 24 hours when a Foley catheter followed by oxytocin is compared to oxytocin alone. However, the use of a Foley catheter has not been evaluated in prospective studies on patients with PPROM.

2.2 Term Induction of Labor

A study on patients at term who are randomized to a Foley catheter combined with Oxytocin vs a Foley catheter alone showed an increased rate of overall delivery and vaginal delivery within 24 hours, and a decrease in total time to delivery, both in nulliparous and multiparous patients (2). Another study in term patients showed that combining a Foley catheter with either Misoprostol or Oxytocin resulted in a shorter time-to-delivery (3).

2.3 Induction of Labor in Patients with Rupture of Membranes

A prospective cohort study in term pregnancies with premature rupture of membranes compared patients receiving Oxytocin vs combination Oxytocin/Foley catheter suggested no difference in vaginal delivery rate between the groups (4). The study also suggested an increased risk of chorioamnionitis when using a Foley catheter, but no difference in other infectious morbidities. However, the study had a mix of term and preterm patients (preterm patients constituted 23% of the Oxytocin/Foley catheter group and 20% of the Oxytocin alone group).

A second study with the same comparison groups showed no difference in median time from induction to delivery, but did not show a difference in infectious morbidity between both groups (5). In this study, preterm patients constituted 13% of the Oxytocin/Foley catheter group and 11% of the Oxytocin alone group.

2.4 Induction of Labor in Patients with PPROM

A retrospective study evaluating Foley catheter use in patients with PPROM did not identify a difference in time-to-delivery and no increased risk of intraamniotic infection (6). However, the study is limited by its retrospective design and large differences between the studied groups (including parity and initial cervical dilation).

There are no prospective randomized trials on the use of transcervical Foley catheter for cervical ripening in patients with PPROM.

2.5 Risk of Infection

While one study showed an increased risk of chorioamnionitis when using a Foley catheter in patients with labor induction, it did not show an increase in neonatal infectious morbidity (4). Additionally, this finding was not replicated in other studies evaluating Foley catheter use in labor induction. A systematic review and meta-analysis addressing this issue concluded that the use of transcervical Foley catheters for cervical ripening and induction of labor is not associated with an increased risk of infectious morbidity (7).

2.6 Rationale for Randomized Trial and Hypothesis

Ripening of the cervix prior to initiation of oxytocin is even more important preterm given that the cervix may be less ripe than at term. Accelerating the time to delivery is also important in preterm premature rupture of membranes in order to prevent adverse outcomes from prolonged induction or chorioamnionitis for both the mother and the preterm infant.

We hypothesize that combination Oxytocin/Foley results in a shorter time to vaginal delivery compared to Oxytocin alone in patients with PPROM and a cervical dilation </=2 cm.

3. Study Design

3.1 Primary Research Question

This randomized trial will address the primary research question:

In patients with preterm prelabor rupture of membranes having an induction of labor, does the addition of a transcervical Foley catheter to IV oxytocin decrease the time to vaginal delivery?

3.2 Secondary Research Questions

Secondary research questions that this study will address are: in patients with PPROM having a labor induction, whether the addition of a transcervical Foley catheter to IV oxytocin improves:

- Overall vaginal delivery rate
- Time from start of induction to active phase of labor
- Composite maternal morbidity, including cesarean delivery and intraamniotic infection;
- Composite neonatal morbidity and mortality, including NICU admission and neonatal infection.

3.3 Design Summary

This study is a non-blinded prospective randomized control trial of pregnant patients with a singleton pregnancy between 34 weeks 0 days and 36 weeks 6 days gestation with PPROM receiving an induction of labor. Participants will be randomized to either:

- Induction of labor with intravenous oxytocin
- Induction of labor with intravenous oxytocin and a transcervical Foley catheter

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

- Patients 18-50 years of age;
- The patient is fluent in English, physically and mentally able to understand the informed consent, and is willing to participate in this study;
- PPROM;
- Cervical dilation </= 2 cm
- Fetal cephalic presentation;
- The patient is between 34 weeks 0 days and 36 weeks 6 days of gestation at the time of enrollment. Gestational age will be determined by last menstrual period, confirmed with a first trimester ultrasound, per the recommended guidelines by the American College of Obstetricians and Gynecologists.

3.4.2 Exclusion Criteria

- Spontaneous labor
- Known allergy to latex;
- Cervical dilation >2 cm;
- Chorioamnionitis;
- Contraindications to induction of labor or use of Foley for cervical ripening
- HIV
- Known or suspected fetal anomaly or aneuploidy;
- Prisoners.

3.5 Informed Consent Criteria

Patients will be approached during admission with a diagnosis of PPROM when they are at ≥ 33 weeks to determine study eligibility.

Written informed consent will be obtained before enrollment into the study. A copy of the consent form will be provided to the patient.

3.6 Randomization Method

Patients will be randomized to either induction of labor with IV oxytocin alone or IV oxytocin combined with a transcervical Foley catheter. Patients will be randomized in a 1:1 ratio using block randomization with opaque envelopes containing the randomized allocated intervention.

4. Study Procedures

4.1 Screening for Eligibility and Consent

Eligible patients will be approached during admission with PPROM when they are ≥33 weeks to determine study eligibility. A member of the study team will approach eligible patients in a private room on the antepartum unit of Sentara Norfolk General Hospital and engage in the process of informed consent with the patient and the patient will sign the consent form if they have agreed to participate in the study.

4.2 Randomization

Patients will be randomized to either induction of labor with IV oxytocin alone or IV oxytocin combined with a transcervical Foley catheter.

4.3 Baseline Procedures

The patient's eligibility information will be collected, including gestational age and estimated date of delivery, in addition to the following:

- Demographics: age, race/ethnicity, insurance status;
- Medical history: pre-pregnancy weight, current weight, height, BMI, most recent blood pressure, past medical history, history of prior preterm delivery, history of cesarean section, history of cerclage placement
- Social history: marital status, years of education, alcohol use, tobacco use and other maternal drug use;
- Obstetrical history: previous miscarriages and terminations, history of pre-eclampsia or other obstetric complications in prior pregnancies.

Patients will be randomized to either induction of labor with IV oxytocin alone or IV oxytocin combined with a transcervical Foley catheter.

IV oxytocin will be administered according to the current Sentara Hospital protocol. A Foley catheter induction involves passing a Foley catheter through the cervix and inflating the Foley catheter balloon to 30 cc.

Patients who are <34 weeks' gestation will be consented during admission, and randomized if and when they require an induction of labor at 34 weeks' gestation. If the patient requires an induction of labor or goes into spontaneous labor prior to 34 weeks, they will not be randomized and not included in the outcome analysis.

4.4 Patient Management and Follow Up

All other obstetric care is at the discretion of the primary provider, including but not limited to: treatment of maternal medical comorbidities or obstetric complications, oxytocin dosing, maternal and fetal surveillance, and need for instrumental delivery or cesarean delivery. Individuals involved with the research will have no part in determining the viability of a neonate.

4.5 Procedures in the Third Trimester, on Labor and Delivery, and Postpartum

Following delivery, study personnel will chart abstract maternal and infant delivery information and maternal and infant data will be collected.

4.6 Adverse Event Reporting

Detailed information concerning adverse events will be collected and evaluated throughout the conduct of the protocol. Adverse events will be reported to the Institutional Review Board per policy.

4.7 Study Outcome Measures

4.7.1 Primary Outcome

The primary outcome is time to vaginal delivery.

4.7.2 Maternal Secondary Outcomes

- Overall vaginal delivery rate;
- Intraamniotic infection
- Operative vaginal delivery and cesarean delivery;
- Estimated and quantitative blood loss;

- Blood transfusion;
- Maternal morbidity and adverse maternal outcomes, including endometritis / chorioamnionitis, wound infection, venous thromboembolism, massive transfusion and postpartum hemorrhage, ICU admission, and maternal death.

4.7.3 Neonatal Secondary Outcomes

- Antepartum, intrapartum, or neonatal death;
- Suspected and confirmed neonatal sepsis
- Intubation, continuous positive airway pressure (CPAP) or high-flow nasal cannula (HFNC) for ventilation or cardiopulmonary resuscitation within first 72 hours;
- Hypoglycemia (glucose < 35 mg/dl) requiring IV glucose therapy;
- Birth weight;
- Neonatal encephalopathy as defined by the NICHD Neonatal Research Network criteria;
- Seizures;
- Shoulder dystocia;
- Birth trauma (bone fractures, brachial plexus palsy, other neurologic injury, retinal hemorrhage, or facial nerve palsy);
- Intracranial hemorrhage (intraventricular hemorrhage, subgaleal hematoma, subdural hematoma, or subarachnoid hematoma)
- Hyperbilirubinemia requiring phototherapy or exchange transfusion
- NICU admission

5, Risks of Participation

- Oxytocin is standardly used for labor induction, and will be administered according to the Sentara Norfolk General Hospital Labor and Delivery Protocol. Participation in this study is therefore unlikely to confer added risk from oxytocin use.
- Transcervical Foley balloons are also standardly used for labor induction in the setting of an unfavorable cervix. Some studies suggested a possible increased risk of intraamniotic infection with transcervical Foley balloon use for induction of labor in the setting of ruptured membranes. However, other studies have refuted this association as discussed in Section 2.5.

5. Statistical Considerations

This randomized control trial will include 80 patients. To determine the appropriate sample size for our study, we employed a Bayesian simulation-based approach using Stata's bayesmh command. The primary outcome variable was modeled as a normally distributed continuous variable, with separate distributions for the control and intervention groups. We assumed that the control group had a mean outcome of 12.6 (SD = 6.4), while the intervention group had a mean outcome of 10.08 (SD = 6.4), representing the expected treatment effect. First a wider range of samples to narrow down the range between 20 and 500 was used. Based on the results, we narrowed down simulation size to a range of sample sizes from 75 to 100 participants to evaluate the impact of sample size on the estimation of the treatment effect. For each sample size, we fit a Bayesian hierarchical model with a normal likelihood and weakly informative priors: a normal(0,10) prior for the group effect and an inversegamma(2,1) prior for the variance parameter. The model was run with two Markov Chain Monte Carlo (MCMC) chains, a burn-in period of 1,000 iterations, and 5,000 post-burn-in samples to ensure convergence. Posterior estimates of the treatment effect, including the mean difference between groups and 95% credible intervals (CrI), were extracted and summarized. The results indicated that, across all sample sizes, the posterior mean difference between groups consistently estimated the expected treatment effect, with credible intervals excluding zero for sufficiently large samples. For example, at n = 100, the posterior mean difference was approximately -2.43, with a 95% CrI of (-4.47, -0.44), suggesting strong evidence of an intervention effect. At n = 75, the posterior mean difference was approximately -1.91, with a 95% CrI of (-4.01, 0.18) suggesting that a larger sample size than 75 will be more appropriate. At a sample size of 78, the posterior mean difference did not cross zero (mean difference = -2.34; 95%CrI = -4.28, -0.16). These findings support our proposed sample size range of 75 to 80 and provide robust Bayesian evidence for detecting meaningful differences between study groups.

A Kaplan-Meier model will be used to compare delivery time, with a pre-planned adjustment for nulliparity and cervical dilation at the time of randomization. A Cox proportional hazard model will be used to compare the time to vaginal delivery between the two labor induction strategies, adjusting for key baseline covariates. Categorical variables will be analyzed using chi-

squared or Fisher's exact as appropriate. Continuous variables will be tested for normality and analyzed using Student's t-test or Mann-Whitney U test as appropriate.

6. Data collection and security

Data collection will be done using REDCap database. Only individuals who are included as investigators or study personnel will be granted access to the database. The REDCap database will NOT include any protected health information; patients will be identified by a unique Study ID. There will be a separate secure database linking Study ID with patient identification. User access will be granted by the PI only. When study personnel/investigators are no longer part of the institution or study, the PI will be notified and their access to the database will be immediately discontinued.

References

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7) McMaster C et al. Evaluation of a transcervical foley catheter as a source of infection: A systematic review and meta-analysis. Obstet gynecol 2015; 539-551