The Effect of Papaverine on Labour in Term Premature Rupture of Membranes (PROM)

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1. Background

Term premature rupture of membranes (PROM), at 37 weeks of gestation or later, occurs in approximately 10% of deliveries and represents a significant clinical challenge. Most women enter labor within 24 hours after rupture of membranes, but some remain in the latent phase of labor, which may increase the risk of infection, prolonged hospitalization, and cesarean delivery. Standard management of term PROM commonly includes induction of labor with oxytocin or prostaglandins; however, these methods are not always effective in inducing labor.

Papaverine, a smooth-muscle relaxant, has been proposed as a potential adjunct to labor induction by promoting cervical softening and improving cervical conditions. In the obstetric induction literature, it has been suggested as an adjunct to mechanical induction. The purpose of this study is to evaluate whether intravenous (IV) papaverine, in combination with oxytocin, can shorten the time to onset/progression of labor and improve maternal and neonatal outcomes among women with term PROM.

2. Rationale

This study aims to evaluate the effectiveness of papaverine in labor induction among women with term PROM. The study will compare papaverine with placebo (physiologic saline) with respect to time to delivery and maternal and neonatal outcomes.

3. Primary Objective

To determine whether intravenous papaverine, administered to women with term rupture of membranes in combination with oxytocin, shortens the time to delivery compared with oxytocin treatment with placebo.

3.1 Secondary Objectives

- To assess the effect of papaverine on mode of delivery (vaginal versus cesarean delivery).
- To evaluate maternal outcomes, including infection rates, postpartum hemorrhage, and additional interventions.
- To evaluate neonatal outcomes, including Apgar scores, umbilical cord pH below 7.1, neonatal infection, and admission to the neonatal intensive care unit (NICU).

4. Primary Outcome

Time to delivery, measured as the interval from intravenous administration of papaverine or placebo until delivery.

4.1 Secondary Outcomes

- Mode of delivery (vaginal or cesarean delivery).
- Cesarean delivery rate.
- Maternal complications (for example, infections and postpartum hemorrhage).
- Neonatal outcomes (for example, Apgar scores, umbilical cord pH, and NICU admission).

5. Methods

5.1 Study Design

This is a randomized, double-blind, placebo-controlled clinical trial. Participants will be randomized in a 1:1 ratio to one of two groups:

- Intervention group: Papaverine 80 mg intravenously in 100 mL of 0.9% saline, administered one hour after initiation of oxytocin.
- Control group: 100 mL of 0.9% saline, administered one hour after initiation of oxytocin.

Allocation will be double-blind. Only one study-team member will be responsible for preparing the study solution with or without papaverine according to the randomization table; the remainder of the team will remain blinded to treatment allocation. In the computerized nursing instructions, the study medication will be documented as "100 mL of 0.9% saline - Papaverine Study."

5.2 Participants, Study Site, and Recruitment

Women hospitalized in the labor and delivery unit because of term rupture of membranes will receive an explanation about the study. If they agree to participate, they will sign informed consent and will then be randomized to one of the two study groups.

Inclusion Criteria

- Age 18 years or older.
- Pregnancy at 37 weeks of gestation or later with term rupture of membranes.
- No active contractions, with cervical dilation <2 cm.
- Vertex presentation.
- PROM duration between 2 and 12 hours.

Exclusion Criteria

- Previous cesarean delivery.
- Contraindication to vaginal delivery.
- Known fetal anomalies.
- Known allergy to papaverine.
- Cardiac arrhythmias, glaucoma, or hepatitis.
- Atrioventricular (AV) block.
- Heart failure.
- Recent ischemic heart disease.
- Increased intracranial pressure.
- Liver disease.
- Active labor (cervical dilation 6 cm).
- Contraindication to uterine relaxation (for example, significant bleeding or fetal distress).
- Active infection or chorioamnionitis.
- Use of medications with potentially hazardous interactions with papaverine (for example, SSRIs, antipsychotic medications, azoles, or clindamycin).

5.3 Variables and Data Collection

Data will be extracted from the hospital computerized records (including Chameleon, Labos, and PACS) and will include:

- Demographic and obstetric data: age, number of previous pregnancies and deliveries, previous cesarean deliveries, pre-pregnancy weight and height, gestational age at delivery, and multiple pregnancy.
- Maternal morbidity: history of gynecologic surgery, history of pregnancy loss, pregnancy complications, elevated blood pressure, smoking, and other relevant conditions.
- Delivery details: time of oxytocin administration, duration of labor induction, duration of contractions/labor, mode of delivery, and complications.
- Neonatal characteristics: birth weight, Apgar scores at 1 and 5 minutes, umbilical cord pH, neonatal complications, neonatal infections, and NICU admission.

5.4 Statistical Methods

Sample Size: Based on previous studies, a clinically significant difference in time to delivery between the groups is expected. With 80% power and a significance level of 0.05, 200 participants will be recruited (100 in each group).

Data Analysis: The primary analysis will compare time to delivery between groups using Student's t test or the Mann-Whitney U test according to the distribution of the data. Secondary analyses will use the chi-square test for categorical variables (for example, mode of delivery) and Student's t test or nonparametric tests for continuous variables (for example, birth weight). Analyses will be conducted according to the intention-to-treat principle.

6. Study Timeline

- Months 1-3: Ethics committee approval and initiation of participant recruitment.
- Months 4-12: Recruitment and enrollment of participants.
- Months 12-18: Data collection and follow-up.
- Months 19-20: Data analysis.
- Month 21: Final report and manuscript preparation.

7. Ethics

Participants will retain the right to withdraw from the study at any time without any effect on their clinical care. All study procedures will comply with Good Clinical Practice (GCP) guidelines.

8. Information and Informed Consent

All participants will receive written and verbal information about the study, including its purpose, procedures, risks, and possible benefits. Written informed consent will be obtained before participation in the study.

Privacy Protection and Confidentiality of Collected Information

Each participant who provides consent to participate in the study will receive a random coded study number representing her identity in the study. Full participant details (identification number, name, and address) will be stored on the password-protected computer of the principal investigator at Edith Wolfson Medical Center, and only the principal investigator will have access to the file containing these identifying details.