# A RANDOMIZED PLACEBO CONTROL TRIAL TO ESTIMATE THE EFFICACY OF ORAL MIFEPRISTONE IN PRE-INDUCTION RIPENING OF CERVIX IN TERM PREGNANCY.

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**KEYWORDS**

Mifepristone, Dinoprostone, Induction of labor, Cervical Ripening.

**ABSTRACT**

**Background:** Cervical ripening is a crucial step in successful labor induction. Mifepristone has emerged as a potential pre-induction cervical ripening agent, but its efficacy needs further investigation.
**Objective:** To evaluate the effectiveness of mifepristone for pre-induction cervical ripening by assessing changes in modified Bishop's score. Secondary objectives included comparing induction-to-delivery intervals, delivery modes, and neonatal intensive care unit (NICU) admission rates.
**Methods:** This randomized, placebo-controlled trial was conducted at the Department of Obstetrics and Gynecology, Karnataka Institute of Medical Sciences, Hubballi, India. We enrolled 232 women with singleton term pregnancies (37-42 weeks gestation) and randomly assigned them to receive either 400mg mifepristone (Group A, n=116) or placebo (500mg calcium tablet) (Group B, n=116). Failed inductions received dinoprostone gel after 24 hours. Modified Bishop's scores were assessed at 0-, 24-, and 48-hours post-administration.
**Results:** Group A demonstrated significant improvement in modified Bishop's score at 24 hours compared to placebo. Only 36% of mifepristone-treated patients required additional induction methods, and the induction-to-delivery interval was reduced by 26.3 hours compared to placebo. Cesarean section rates were comparable between groups. No significant differences in maternal or perinatal morbidity and mortality were observed between groups.
**Conclusion:** Mifepristone demonstrates significant efficacy as a pre-induction cervical ripening agent in term pregnancies, reducing the need for additional induction methods and shortening the induction-to-delivery interval without increasing adverse outcomes.

## INTRODUCTION

The cervix serves as the female reproductive system's entrance. The appropriate mechanical function of uterine cervix is critical for maintaining a pregnancy to term so that fetus can develop fully. Cervix must significantly soften, shorten, and dilate inorder to facilitate delivery.

Induction of labor can be defined as an intervention to artificially initiate uterine contractions resulting in progressive effacement and dilatation of the cervix.

The changes in the uterine cervix that take place before the onset of labor include physically detectable softening, shortening and dilatation of the OS. This process is called ripening.

Success of ripening is assessed by pre and post induction Modified Bishop scores. Mifepristone, when compared to mechanical methods, reduces induction delivery interval, risk of infection, bleeding, early membrane rupture. When compared to placebo, it is said to have more effects in increasing the chances of spontaneous labor and reducing the need for prostaglandins.

Hence this study aims to know the efficacy of oral mifepristone in pre-induction cervical ripening of labor in term pregnancy.

**Objective**:

**Primary objective**: Changes in modified Bishop's score in preinduction and post induction.

**Secondary objective**: Induction to delivery time interval, mode of delivery and need for NICU admission.

## MATERIALS AND METHODS

- **Study Population:** All PW visiting our tertiary center OPD/ labor room/ admitted in ward were considered
- **Study Design:** Randomized placebo Controlled Trial.
- **Site of the Study:** Karnataka Institute of Medical Sciences, Hubballi, Karnataka, India.
- **Study Duration**:18 months

**Methods of data collection:** Proforma was created and attached to the case paper of the PW, which was entered prospectively.

**Inclusion criteria:**

- Singleton pregnancy
- Term gestation (37-42weeks)
- Cephalic presentation
- Intact membranes
- Adequate liquor
- Reactive fetal heart rate pattern in CTG
- Adequate pelvis
- Unfavorable cervix with Modified Bishop's score <6

**Exclusion criteria:**

- Presence of medical disorders like Cardiovascular, renal, hepatic disease, and asthma.
- Presence of obstetric complications like Cases of severe pregnancy induced hypertension, Abruption
- Any contraindication for vaginal delivery or mifepristone.
- Any known Hypersensitivity to mifepristone.

**Sample size:** This is a Randomized Placebo Controlled Trial. The sample size was 232 women with 90% power of study and 2.5% two-sided alpha error. The required sample size was calculated using the formula as proposed by Kirkood BR et al[4].

**Method of study:** All PW with term singleton pregnancy were recruited as per inclusion criteria and randomly allocated into two groups – group A and group B by lottery method PW assigned to group A (n= 116) received a single dose tablet mifepristone 400mg orally and PW assigned to group B (n= 116) received placebo (tablet calcium 500mg orally). Modified Bishop's score was assessed at the end of 0/ 24/ 48 hours.Women who did not enter labor following induction, labor induction was planned with intracervical instillation of dinoprostone gel 8$^{th}$ hourly for a maximum of three doses. Primary objective and secondary objectives of both the groups were noted.

**RESULTS:**

**Changes in the modified Bishop's score**

**Table 1:** Comparison of changes in modified Bishop's scores between cases and controls at admission, 24hrs and 48hrs treatment times by independent t test

| Time in hours | Mifepristone only (n= 74) | Mifepristone f/b dinoprostone gel (n= 42) | Placebo f/b dinoprostone gel | z value | p value |
|---|---|---|---|---|---|
| 0 | 3.5 | 2.73 | 3.38 | 0.793 | >0.05 Not significant |
| 24 | **11.5** | **5.16** | 3.38 | 14.09 | <0.001 significant |
| 48 | 14.4 | 10.59 | 13.96 | 2.26 | <0.05 significant |

*p<0.05

**Impression :**The modified Bishop's score at admission were comparable between two groups. At the end of 24 hours, the cases primed with tablet mifepristone showed favorable score.(statistically significant). At the end of 48 hours the modified Bishop's score between the two groups were comparable.

**2. Need for induction after 24 hrs.:** 64% of cases in group A did not require additional doses of induction. All the cases in group B required induction after 24 hours,

**Table 2:** Need for induction after 24 hrs in group A and group B.

| Need for induction after 24 hrs | Group A | Group B |
|---|---|---|
| Yes | 42(36%) | 116(100%) |
| No | 74(64%) | 0 |

**3.Induction delivery interval**

**Table 3 :** Induction delivery interval

| Induction delivery interval | Group A | Group B |
|---|---|---|
| Mifepristone – delivery interval | 23.9 hrs | |
| Mifepristone – dinoprostone – delivery interval | 32.3 hrs | |
| Placebo– dinoprostone– delivery interval | | 50.2 hrs |
| dinoprostone – delivery interval | | 26.7 hrs |

The cases delivered on an average within 24 hours of mifepristone, those requiring induction required additional 8 hours.

**4. Mode of delivery**

**Table 4:** Mode of delivery in group A and group B

| MODE OF DELIVERY | Group A | Group B |
|---|---|---|
| Vaginal | 90% (n= 104) | 93% (n= 109) |
| LSCS | 12(10%) | 7 (6%) |

90% of cases in group A and 93% of group B delivered vaginally. Mode of delivery was comparable between the two groups.

**5. Indication of LSCS:** There was equal number of failed inductions in each group (2 each). Fetal distress cases were 6 and 4 respectively. Among the 12 cases in group A 11 cases were primigravida and 1 was multiparous, indication being failed induction in the later.

In group B, 5 cases were primigravida and 2 cases were multiparous, indication being failed induction and fetal distress in the later.

**6. Perinatal outcomes**

**Table** 5: Perinatal outcomes in group A and group B

| **APGAR SCORES** | **Group A** | **Group B** | **Z value** | **p value** |
|---|---|---|---|---|
| **APGAR at1min** | **7.96 ±1.130** | **7.72 ± 0.921** | **1.783** | **>0.05** |
| **APGAR at 1min** | **8.93 ± 1.284** | **8.68 ± 1.001** | **1.654** | **>0.05** |

**Table** 6: Perinatal outcomes in group A and group B

| **Clinical Output** | Description | Group A (n= 100) | Group B (n = 125) |
|---|---|---|---|
| **NICU admission** | Need for NICU admission | 17 | 17 |
| **Perinatal mortality** | Death | 2 (1.7%) | 1 (0.8%) |

The perinatal outcomes between the two groups were comparable.

**7. Maternal third stage complications:**

Atonic PPH were comparable between group A and B. 3 cases in group A and 1 in group B. All cases were managed medically. No other significant complications were noted**.**

**DISCUSSION**

It is yet unknown how labor is initiated. Progesterone, however, is well known to havea crucial role in maintaining pregnancy. Anti-progestin exposure during pregnancy is thought to hasten the start of parturition.

Mifepristone is a novel antiprogestin. Initially it was used as an abortificient in medical termination of pregnancy. Later it was used in induction for termination of intrauterinefetal demise, which has inspired others to research mifepristone's impact on term pregnancies. Various studies have been conducted to know the effect of mifepristone in cervical ripening and induction of term live pregnancy.

**Demographic details and Gravidity:** There were equal number primi (55%) and multiparous (45%) among the two groups, comparable with study by Chinniah R.et al, Mohapatra et al.[1]Similar to the study conducted by Deepika N.et al[5] (where study group received tablet Mifepristone 400mg and control group female received placebo).

**Pre induction modified Bishop's score:** The mean modified Bishop's score at inclusion was 3.28 in group A which was comparable to the studies by Mohapatra S. et al[1] where the mean modified Bishop's score at the outset was 3.27 and Saranya[6] and Yellikar et al[7], where the mean modified Bishop's score at the outset was 2.72. Improvement in modified Bishop score after 48hours in the 2 groups were comparable. In contrast, Sailatha et al's[8] study value found that the improvement in modified Bishop's score was noticeably greater in the dinoprostone group compared to the mifepristone group.

**Need for additional induction agent:** 36% PW of group A needed additional induction, here in the form of dinoprostone gel while 67% delivered only with tablet mifepristone. One dosage of dinoprostone was needed in 16% of PW of group A and 58% of PW of group B. Two doses of dinoprostone were necessary in 10% of group A and 27% of group B. Three doses of dinoprostone gel were needed in 7% of group A and 15% of group B.

**Mode of delivery:** Rate of cesarean delivery was comparable between group A (10%) and group B (6%). Gaikwad et al[9] found higher incidence of LSCS in dinoprostone group. In our study we had an equal number of failed inductions. The most common indication for LSCS was fetal distress among the groups. In a study by Mohapatra et al[1], the rate of LSCS in the mifepristone group was 8% and 16% in the other group. Deepika N.et al's[5] study showed that rate of caesareans was in 10% women in mifepristone group and 20% in control group. In all these studies 200mg mifepristone was used in contrast to our study where 400mg mifepristone was used. The current study and studies by Chourasia U.[3] et al. found no significant difference in the mode of deliverybetween study and control group.

**Intrapartum complications:** Comparable to Mohapatra et al.[1], neither of the group A in our study nor group B patients exhibited hypertonus or tachysystole.

**Maternal and perinatal complications:** Mifepristone did not cause any adverse maternal and perinatal outcomes in our study. Perinatal mortality in both group A and group B were due to birth asphyxia. Neonatal outcomes in both the groups were comparable with Yelikar et al[7]. According to Dhillon P.[11] et al, neonatal complications and neonataladmissions were lesser in the mifepristone group. Study by Deepika N.et al[5] showed patients having minor gastrointestinal sideeffects in form of nausea, vomiting, hyperthermia, headache and sweating.

**LIMITATIONS:** Instead of assessment of modified Bishop's score to know the effect of induction agent, induction to onset of active (4-5 cm cervix) labor interval should have been assessed. But we assessed changes in Modified Bishop's score at predefined intervals to reduce the number of unindicated per vaginal examinations.

**CONCLUSION:** Mifepristone is an effective agent for cervical ripening and inducing agents. It reduces the requirement for additional induction and doses of inducing agents.

**Declarations:**
**CTRI Registration**: CTRI/2021/04/033044
**Conflict of Interest**: there is no conflict of interest involved in this study.
**Ethical approval**: Ethical clearance was taken for the study.
**Informed consent**: Patient consent was taken.
**Funding:** We utilized the infrastructure, medicines and facilities of our institute, it was free to all the PW.

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