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# Study of Safety and Efficacy of Mifepristone with Misoprostol and Misoprostol Alone in Induction of Labor in Term Pregnancy

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**ABSTRACT**

Induced Labor is one in which pregnancy is terminated artificially, any time after fetal viability is attained by a method that aims to secure vaginal delivery. Different methods which are widely used for labor induction are vaginal prostaglandins, intracervical prostaglandins, intravenous oxytocin, extra amniotic Foley's catheterization. Present study was aimed to assess the efficacy of combination of Mifepristone and Misoprostol with respect to Misoprostol alone for induction of labor. Present study was single-center, prospective, observational study, conducted in pregnant women, singleton pregnancy, cephalic presentation, unfavorable cervix with bishops score <6, reactive FHR pattern with intact membranes, with gestational age between 37 weeks till 41 weeks of gestation requiring induction of labour for various indications. 200 women were divided GROUP A- Mifepristone followed by Misoprostol group and GROUP B-Misoprostol group. In group A patients, mean Bishop's score after receiving tablet Mifepristone, increased from 2.23-4.95. Mean induction to active stage interval, mean induction-delivery interval, requirement of Misoprostol and Requirement for augmentation with oxytocin was less in group A as compared to group B, difference was statistically significant. The incidence of vaginal delivery was slightly higher in group A (70%) versus group B (30%), difference was statistically significant. Outcome of induction of labor in both the groups with success rate of 94 and 95%, no significant difference was noted. NICU admissions were more in group B (14%) as compared to group A (8%). Mifepristone(with or without Misoprostol). Mifepristone along with or without Misoprostol is a safe, effective and convenient alternative to Misoprostol alone in induction of labor in women at term.

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**Key Words**
Induction of labour, Misoprostol, Mifepristone, term pregnancy

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## INTRODUCTION

Induced Labor is one in which pregnancy is terminated artificially, any time after fetal viability is attained by a method that aims to secure vaginal delivery. The primary condition that must be fulfilled to interfere with this natural process must be that benefits of terminating pregnancy for the mother or her fetus or both, clearly outweigh the potential harms. Penalties of failure and hazards of prolonged labor have been recognized for centuries and have influenced thinking in obstetrics right up to the present[1].

Different methods which are widely used for labor induction are vaginal prostaglandins, intracervical prostaglandins, intravenous oxytocin, extra amniotic Foley's catheterization. Mifepristone is an antiprogestin which can be used 24-48 hrs before the prostaglandin administration. Misoprostol is a PGE1 analog. The combination of Mifepristone and Misoprostol is now established and highly effective and safe method for termination of first and second trimester pregnancies[2].

The combination significantly reduces induction to abortion interval and also has fewer adverse effects, complications and also reduces the dose of Misoprostol. In cases where Mifepristone is not available or affordable, Misoprostol is also effective but a higher dose is needed and efficacy is lower than the combined regimen[3]. In our country not many studies have been done regarding the combined regimen for induction of labor in term pregnancies. Present study was aimed to assess the efficacy of combination of Mifepristone and Misoprostol with respect to Misoprostol alone for induction of labor.

## MATERIALS AND METHODS

Present study was single-center, prospective, observational study, conducted in department of obstetrics and gynecology, at XXX medical college & hospital, XXX, India. Study duration was of 2 years (October 2019 to September 2021). Study approval was obtained from institutional ethical committee.

**Inclusion criteria:** Pregnant women, singleton pregnancy, cephalic presentation, unfavorable cervix with bishops score <6, reactive FHR pattern with intact membranes, with gestational age between 37 weeks till 41 weeks of gestation requiring induction of labour for various indications, willing to participate in present study

**Exclusion criteria:**

- Previous uterine surgeries (caesarean section, myomectomy and other scar)
- Multiple pregnancy
- Pregnancy with any medical or surgical complications
- Malpresentation
- Women not giving consent for study
- Subjects with known hypersensitivity to either Mifepristone (presence of adrenal failure long term oral corticosteroid therapy, hemorrhagic disorders, inherited porphyria and haemophilia or anticoagulant use or Misoprostol or both

Study was explained to patients in local language and written consent was taken for participation and study. A total of 200 women in the gestational age group of 37-41 weeks were enrolled in the study. They were divided into two groups:

- **Group A:** Mifepristone followed by Misoprostol group
- **Group B:** Misoprostol group

Every alternate patient was assigned to each group. After obtaining written informed consent these patients were enrolled in present study. Information regarding the dose of drugs, their side effects, need for surgical intervention were told in details. Informed written consent was taken after giving complete information about the procedure. A detailed per abdominal and per vaginal examination was conducted. Hematological investigations like CBC, blood group, HIV, HBsAG along with USG, NST were done.

**Group A: Mifepristone followed by misoprostol:** Hundred patients received 200 mg of Mifepristone for pre induction cervical ripening after assessing Bishop's score and induced with 25 mcg of vaginal misoprostol after 48 hrs. Bishops score was reassessed at 48 hrs before giving tablet Misoprostol. Misoprostol was repeated every 4-6 hourly till patient went into active labour for a maximum of four doses after assessing uterine contractions and cervical dilatation and effacement. Number of women entering into labour with Mifepristone alone was also noted.

**Group B: Misoprostol:** Hundred patients received 25 mcg of misoprostol per vaginally which was repeated every 4-6 hrs till patient went into active labour for a maximum of 4 doses as required .Bishop score was assessed every 4 hrs. In case of further augmentation in both the groups, protocols in the Department (oxytocin) were followed

After administration of drugs, patients were monitored for signs of labour, maternal vitals, FHR and progress of labour. Labour and delivery parameters

including induction to delivery interval, number of doses of misoprostol required until delivery, mode of delivery was noted in both groups. Occurrence of fever, gastrointestinal symptoms, hyperstimulation, PPH was noted. Fetal criteria including meconium staining of liquor, fetal distress as defined by abnormal CTG requiring prompt emergency delivery, APGAR scores at 1 and 5 min, meconium aspiration and transfer to NICU was noted.

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi- square test or Fisher exact test as applicable. The $p<0.5$ was considered as statistically significant.

## RESULTS

In present study, total of 200 women were equally divided in group A and group B. Maximum number of study subjects were from age group of 26-30 years (58%) in Group A and Group B (46%), followed by age group 21-25 years in group A (40%) and in group B (40%). Primigravida in group A (54%) were more than group B (49%). Majority patients had completed gestational age of 40 weeks (group A: 42%, group B: 54%) (Table 1).

In group A patients, mean Bishop's score after receiving tablet Mifepristone, increased from 2.23-4.95 (Table 2).

Mean induction to active stage interval was (7.5±3.082 hrs) less in group A as compared to group B (9±2.811), difference was statistically significant. The Mean induction- delivery interval was (11.5±4.58 hrs) less in group A as compared to group B (13.33±3.814), difference was statistically significant. The requirement of Misoprostol was higher in group B (2.44) as compared to group A (1.95) and difference was statistically significant. Requirement for augmentation with oxytocin was significantly higher in group B(56%) as compared to group A (40%) (Table 3).

The incidence of vaginal delivery was slightly higher in group A (70%) versus group B (30%), difference was statistically significant. The incidence of caesarean section was slightly higher in group B (34%) versus group A (30%). Out of 70% patients who delivered vaginally, 19 patients (27.14%) delivered with induction with Mifepristone only. Common indications for LSCS were fetal distress and FHR irregularities.

The incidence of maternal side effects was significantly less in group A as compared to group B. Group A had 1 case of vomiting, atonic PPH and traumatic PPH each, whereas there were 11 cases of vomiting, 4 cases of fever, 3 cases of atonic PPH and diarrhea each and 2 cases of uterine hyperstimulation (Table 4).

Outcome of induction of labor in both the groups with success rate of 94 and 95%, no significant difference was noted (Table 5).

NICU admissions were more in group B (14%) as compared to group A (8%). There were no perinatal deaths seen in either groups. APGAR score at 1 min was almost same, with 11 and 12% patients having score $\leq$6 in group A and B respectively. In group A, APGAR score at 5mins was $\leq$8 in 32% patients while it was higher, 41% patients in group B (Table 6).

## DISCUSSIONS

Induction of labor is unique in medicine as it seeks to advance a process which in the natural course of events is inevitable unless the pregnancy is terminated by caesarean section or the mother and fetus ends up in adverse outcome. According to most current studies the rate of induction of labor varies from 9.5-33.7% of all pregnancies annually[4]. Induction of

Table 1: General characteristics

| Characteristics | Group A | Group B | Total | chi-square | p-value |
|---|---|---|---|---|---|
| **Age groups (years)** | | | | | |
| <20 years | 1 | 4 | 5 | 4.526 | 0.204 |
| 21-25 years | 40 | 47 | 87 | | |
| 26-30 years | 58 | 46 | 104 | | |
| 31-35 years | 1 | 3 | 4 | | |
| **Gravida** | | | | | |
| Primi | 54 | 49 | 103 | 0.5 | 0.572 |
| Multi | 46 | 51 | 97 | | |
| **Gestational age (weeks)** | | | | | |
| 37 completed | 8 | 5 | 13 | 3.38 | 0.06 |
| 38 completed | 25 | 20 | 45 | | |
| 39 completed | 25 | 20 | 45 | | |
| 40 completed | 41 | 49 | 90 | | |
| >40 completed | 1 | 6 | 7 | | |

Table 2: Changes in bishop's score in patients of group A after giving Mifepristone

| | Group A | |
|---|---|---|
| Bishop's score | Mean | Standard deviation |
| Pre induction score | 2.23 | 0.888 |
| 48 hrs | 4.95 | 0.757 |

Table 3: Labour characteristics

| Characteristics | Group A | Group B | Chi-square | p-value |
|---|---|---|---|---|
| **Induction to active stage** | | | | |
| 0-6 hrs | 25 | 27 | 0.038 | 1.00 |
| 7-12 hrs | 42 | 51 | | |
| 12-18 hrs | 3 | 6 | | |
| Total | 70 | 84 | | |
| Mean±SD | 7.5±3.082 | 9.0±2.811 | 3.15 | 0.0019 |
| **Induction delivery interval** | | | | |
| 4-8 hrs | 25 | 14 | 10.59 | <0.001 |
| 9-12 hrs | 25 | 38 | | |
| 13-16 hrs | 21 | 31 | | |
| 17-20 hrs | 5 | 14 | | |
| 21-24 hrs | 5 | 3 | | |
| Total | 81 | 100 | | |
| Mean±SD | 11.50±4.58 | 13.33±3.814 | 2.933 | <0.001 |
| **Doses of misoprostol** | | | | |
| 0 | 19 | 0 | 21.27 | <0.001 |
| 1 | 17 | 19 | | |
| 2 | 27 | 33 | | |
| 3 | 24 | 33 | | |
| 4 | 13 | 15 | | |
| Mean | 1.95 | 2.44 | | |
| **Oxytocin augmentation** | | | | |
| Yes | 40 | 56 | 5.128 | 0.024 |
| No | 60 | 44 | | |
| Mode of delivery | | | | |
| LSCS | 30 | 34 | 0.368 | 0.544 |
| Vaginal | 70 | 66 | | |
| **Indication** | | | | |
| Fetal distress | 17 | 17 | 4.014 | 0.56 |
| Failed induction | 6 | 9 | | |
| Non progression of labour | 4 | 2 | | |
| FHR irregularities | 3 | 6 | | |

Table 4: Distribution of study subjects according to maternal side effects

| Adverse drug outcome | Group A | Group B | Fisher exact | p-value |
|---|---|---|---|---|
| None | 97 | 77 | 21.07 | <0.001 |
| Vomiting | 1 | 11 | | |
| Fever | 0 | 4 | | |
| Diarrhea | 0 | 3 | | |
| Atonic PPH | 1 | 3 | | |
| Traumatic PPH | 1 | 0 | | |
| Uterine hyperstimulation | 0 | 2 | | |

Table 5: Outcome of in duction of labor

| Outcome | Group A | Group B | Chi square | p-value |
|---|---|---|---|---|
| Success | 94 | 95 | 0.0962 | 0.756 |
| Failure | 6 | 5 | | |

Table 6: Distribution of study subjects according to perinatal outcome

| NICU admission | Group A | Group B | Chi- square | p-value |
|---|---|---|---|---|
| Yes | 8 | 14 | 1.839 | 0.175 |
| No | 92 | 86 | | |
| **APGAR score at 1 min** | | | | |
| ≤6 | 11 | 12 | 0.049 | 1 |
| >6 | 89 | 88 | | |
| **APGAR score at 5 min** | | | | |
| ≤8 | 32 | 41 | 1.747 | 0.186 |
| >8 | 68 | 59 | | |

labor is one of the important tools in an obstetrician's armamentarium as he/she can intervene and induce labor as may be indicated for maternal or fetal interest or both[5].

Mifepristone an antiprogestin is being used to stop the action of progesterone either to terminate pregnancy or to induce labor. In our study, Mifepristone 200 mg tablet was used. Byrne *et al*.[6] demonstrated that Mifepristone exposure and induced labor was associated with increase in cortisol levels and significant elevation in cortisol levels was observed within 18 hrs of exposure to Mifepristone. Hapangama and Neilson[7] reported that there is insufficient evidence to support a particular dose but a single dose of 200 mg Mifepristone appears to be the lowest effective dose dose for cervical ripening.

The incidence of nulliparity was 54 and 49% respectively in Group A and B. The distribution of pregnancies did not differ significantly between the two groups which was comparable to Frydman *et al*.[8], Stenlund *et al*.[9] and Deepika *et al*.[10].

In the p resent study, the mean Bishop's score at 0 hr of induction with Mifepristone is 2.23, whereas the mean Bishop's score at 48 hrs of induction with Mifepristone is 4.95. The results of our study are comparable to study conducted by Yelikar *et al*.[11] in

which the mean Bishop's score at 0 hr in Mifepristone group was 2.02±0.749, whereas mean Bishop's score at the end of 24 hrs was 5.0408±1.90. The results of our study are also comparable to study conducted by Mandade *et al*.[2] in which the mean Bishop's score at 0 hour of induction was 3.84±1.03 in study group and 8.54±2.06 at the end of 48 hrs.

In our study 19% patients of Mifepristone group went into labor and delivered vaginally without any need of Misoprostol. Similar findings were reported by Yelikar *et al*.[11] where 16% patients in Mifepristone group went into labor and delivered vaginally without any need of Misoprostol.

The time interval between induction with first dose of Misoprostol and delivery is considered as induction-delivery interval. In the present study induction-delivery interval is 11.50±4.58 hrs in group A and 13.33±3.814 hrs in group B. The difference is statistically significant indicating that Mifepristone is an efficient inducing agent in term pregnancy which is comparable to Stenlund *et al*.[9] and Wing *et al*.[12]. The results of our study is comparable to study conducted by Mandade *et al*.[2], in which mean induction-delivery interval was 9.34±2.81 hrs in Mifepristone followed by Misoprostol group and 10.94±3.98 hrs in only Misoprostol group, the difference being statistically significant.

In the present study, we found statistically significant decrease in the requirement of Misoprostol with prior use of Mifepristone. The mean dose of Misoprostol required in group A was 1.95 whereas, the mean dose of Misoprostol required in group B was 2.44, the difference being statistically significant.

Similar results were seen in study conducted by Mandade *et al*.[2], the mean doses of Misoprostol required was 1.4±0.8 in group A and 2.14±0.6 in group B. The difference was statistically significant. Likewise, Yelikar *et al*.[11] also reported a decrease in the requirement of Misoprostol with prior use of Mifepristone. The findings were statistically significant. Wing[12] also reported reduction in need of prostaglandin/oxytocin in Mifepristone group.

In study conducted by Mandade and Bangal[2], 86% subjects in group A and 78% subjects in group B delivered vaginally and 12 % subjects in group A and 16% subjects in group B required LSCS. In the study conducted by Deepika *et al*.[10] 10% of women in group A and 20% in group B underwent cesarean section. Similar findings were noted in present study.

In the present study, 40% of subjects required augmentation with Oxytocin in group A whereas, 56% of study subjects required Oxytocin in group B. The difference is statistically significant. Our results corroborated well with the study conducted by Mandade and Bangal[2] in which the need for oxytocin for augmentation of labor was significantly more (84%)in MIFE+MISO group which was proven statistically significant. Wing *et al*.[12] also reported reduction in need of prostaglandin/oxytocin in Mifepristone group. Hapangama and Neilson[7] also reported that Mifepristone treated women were less likely to need augmentation with oxytocin.

In the present study, fewer maternal side effects were observed in group A as compared to group B. Group A had 1 case of vomiting, atonic PPH and traumatic PPH each, whereas there were 11 cases of vomiting,4 cases of fever, 3 cases of atonic PPH and diarrhea in group B which is statistically significant. Cases of atonic PPH got managed with medical line. Surgical management was not required.

Mandade and Bangal[2] in their study also reported a reduced incidence of adverse reactions in group A as compared to group B though the findings were not statistically significant. Other complications observed were tachysystole and fetal heart variability, more with only Misoprostol group. Yelikar *et al*.[11] also reported a less incidence of PPH, tachysystole and hyperstimulation in Mifepristone+Misoprostol group.

In our study, there was no significant difference as regards to outcome of induction between both the groups. Findings of our study are similar to Yelikar *et al*.[11] who also reported a success rate of 94% of induction in Mifepristone group. The rate of successful induction of 94% in our study is also comparable with Wing[12].

In our study, there was no significant difference in number of NICU admissions in both the groups though the incidence was higher in group B (14%) versus group A (8%). According to Fathima *et al*.[13] also there is no significant difference in perinatal morbidity. Wing[12] observed 13.4% incidence of NICU admission with APGAR score <7 at 1 min in Mifepristone only induction protocol which was not significant when compared to control group. Yelikar *et al*.[11] and Hapangama and Neilson[7] also reported no significant difference in neonatal outcome.

## CONCLUSION

Mean induction to active stage, mean induction to delivery, requirement of subsequent doses of Misoprostol, augmentation of labor with Oxytocin, incidence of cesarean section and side effects experienced by study subjects were significantly lower in subjects receiving Mifepristone (with or without Misoprostol). Mifepristone along with or without Misoprostol is a safe, effective and convenient alternative to Misoprostol alone in induction of labor in women at term.

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