Comparative study between mifepristone and dinoprostone gel for cervical ripening and induction of labour

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Abstract---Induction of labor is common in obstetric practice. According to the most current studies, the rate varies from 9.5 to 33.7 percent of all pregnancies annually. Cervical ripening is necessary for a successful vaginal delivery. This study shows shorter labour stages I and III, and less blood loss in mifepristone group. The drug has no significant effects on uterine contraction and no serious maternal complications. This drug has a safe neonatal outcome. Patient can remain ambulatory, which is very convenient as compared to PGE2 gel. PgE2 gel needs refrigerator for storage and skill for intracervical insertion with strict aseptic technique. Hence mifepristone offers advantages over PGE2 gel which is currently used for preinduction cervical ripening.

Keywords---mifepristone, dinoprostone gel, cervical ripening, induction of labour.

Introduction

Induction of labor is common in obstetric practice. According to the most current studies, the rate varies from 9.5 to 33.7 percent of all pregnancies annually. Cervical ripening is necessary for a successful vaginal delivery. Therefore, cervical ripening or preparedness for induction should be assessed before a regimen is selected. Assessment is accomplished by calculating a Bishop score. When the Bishop score is less than 6, it is recommended that a cervical ripening agent be used before labor induction. 1-2

Nonpharmacologic approaches to cervical ripening and labor induction have included herbal compounds, castor oil, hot baths, enemas, sexual intercourse,
breast stimulation, acupuncture, acupressure, transcutaneous nerve stimulation, and mechanical and surgical modalities. Of these nonpharmacologic methods, only the mechanical and surgical methods have proven efficacy for cervical ripening or induction of labor. Pharmacologic agents available for cervical ripening and labor induction include prostaglandins, misoprostol, mifepristone, and relaxin. When the Bishop score is favorable, the preferred pharmacologic agent is oxytocin.\textsuperscript{3-4}

Presently, there is a lot of difference in the choice of inducing agent. Variation depends upon the efficacy of agent, risk/benefit ratio, institutional protocol, FDA approval, availability of drugs, cost-effectiveness, and obstetrician choice preference. Commonly used drugs for the induction of labor are prostaglandin analogues such as dinoprostone and misoprostol. Mifepristone/RU-486, a new class of pharmacological drug, has been developed to antagonize the action of progesterone. It is the 19 norsteroid, which has greater affinity for progesterone receptor than does progesterone itself. It blocks the action of progesterone at the cellular level.\textsuperscript{5-6}

Mifepristone is a steroidal compound that has antiglucocorticoid and antiprogestosterone properties. Progesterone stops uterine contractions, so mifepristone is used to stop the action of this hormone; thus, it induces the labor or allows the pregnancy to be terminated. Mifepristone is proving to be a promising drug for inducing labor in late pregnancy through its anti progestin action, which increases uterine contractility and sensitivity of uterus to the action of prostaglandins.\textsuperscript{7}

Prostaglandin E2 (PGE2) has been recognized as one of the successful agents for labor induction, which is effective not only in achieving cervical ripening but also in activating myometrial contractility. Success of labor induction is related to the state of cervix. Women with unfavorable cervix, who have not experienced cervical ripening phase before labor, present the greatest challenge with regard to labor induction.\textsuperscript{8-10}

Hence the present study was conducted at a tertiary healthcare teaching institute to compare the efficacy and safety profile of Mifepristone with dinoprostone gel for induction of labor in term pregnancies with unfavourable cervix and intact membranes.

**Material and Methods**

It was a Cross sectional randomized comparative study, conducted during November 2019 till May 2021, at Krishna Institute of Medical Sciences, Karad, Maharashtra, Using Computer generated Random sequence. Patients who were undergoing induction and delivery in the Department of Obstetric and Gynaecology at Krishna Institute of Medical Sciences, Karad, Maharashtra. Patients were grouped into two groups, one received Mifepristone and other group received Dinoprostone Gel for cervical ripening and induction of labour. Assignment of either of the two groups were based on computer generated random sequence.
Inclusion criteria: Subjects with Gestational age > 37 weeks, Single Live Intrarudine gestation with Cephalic presentation and intact membranes where labour induction is indicated and delivery can be postponed for 24 hours, Reactive NST pattern in live fetus, and Bishop score < 6 were included in the present study.

Exclusion criteria: Subjects with Estimated fetal weight > 4500 gm or < 2000 gm, Previous cesarean, Antepartum hemorrhage, Chorioamnionitis, CPD, macrosomia, malpresentation, Premature rupture of membrane, Known hypersensitivity to mifepristone, Parity > 4, and Medical problems like impaired renal, hepatic or adrenal function were excluded from the present study.

Sample size estimation: According to a similar study conducted by Sailatha R et al.[ref] the mean and standard deviation of induction delivery interval in hours was 20.3 ± 15 Hr and 11.5 ± 8.7 Hr respectively in the two groups. Using the formula to calculate sample size for each comparative group in the studies with comparison between the groups. The notation for the formulae are:

\[ n_1 = \text{sample size of Group 1}, \quad n_2 = \text{sample size of Group 2}. \]
\[ \text{Where standard deviation of Group 1 = 15, and standard deviation of Group 2 = 8.7, Difference in group means} = 20.3 - 11.5 = 8.8, \text{ratio} = n_2/n_1 = 1, \quad Z_1 = 1.96 \text{ for 95% confidence interval, } \]
\[ Z_1 = \text{two-sided Z value} \]
\[ Z_1 = \text{power}. \]

So for comparing the 2 groups minimum sample size in each group should be 31.

Total sample size is, \( N = n_1 + n_2 = 31 + 31 = 62 \). Hence Minimum 62 patients are to be included in the study, rounding it to 80. So, we considered total 80 patients in our study, 40 from each comparative group.

GROUP A: Group A received 200 mg Mifepristone orally, Bishop score was assessed pre induction and post induction after 24 hours or at onset of labour whichever is earlier, and if the score is 6 or more labour may be augmented with Oxytocin or amniotomy

GROUP B: Group B received 0.5 mg Dinoprostone intracervically just below the level of internal os, with instruction to remain recumbent for 30 mins, Fetal heart rate and contractions was monitored according to the hospital protocol, Bishop score is to be assessed 6 hours after Induction, If Bishop score is more than 6 oxytocin augmentation was started, and if Bishop score is less than 6 0.5 mg Dinoprostone was reinstilled

**Statistical analysis**

Data was collected using a semi structured, pretested, prevalidated, standard questionnaire. Data Collected was entered in Microsoft Excel data sheets. Data was represented in frequencies and percentages, charts and graphs for frequency analysis. Mean and standard deviation of quantitative variables were shown. Appropriate statistical tests were applied using SPSS software version 20 and Epi Info 7.2.1 for analysis. Chi square test was used to study association between qualitative variables and student’s t-test was used for comparison between the
two groups with quantitative variables. Other statistical tests were used as per the study requirements. A p value of <0.05 were considered significant in our study results.

Results

Demographic information

In the present study we assessed the age distribution of the study subjects. We observed that majority of the study subjects belonged to the age group of 26 to 35 years (55% and 50% in either group), followed by more than 36 years (37.5% and 40% resp). (Table 1)

Gravida: In this study we assessed the gravida status among the study subjects. We observed that majority were primigravida (72.5% and 62.5 resp). (Table 1)

Bishops score: In the present study we assessed the Bishops score at the start. We observed that majority of the subjects had score of 3 (70% and 62.5% resp), followed by score 2 (25% and 30% resp). In the present study we assessed the Bishops score at augmentation. We observed that majority of the subjects had score more than 6 (57.5% and 52.5% resp in both study groups). The difference between the observations in either groups was not found to be statistically significant. (The chisquare statistic is 0.202. The p-value is .653095. Not significant at p < .05.) (Table 1)

Oxytocin augmentation: In the present study we assessed the need of oxytocin augmentation among the study subjects. We observed that oxytocin augmentation was required significantly more among mifepristone group (90%), as compared to dinoprostone group (70%). (The chi-square statistic is 5. The p-value is .025347. Significant at p < .05.) (Table 1)

Duration of labour (In minutes): In the current study we assessed the duration of labour among the study subjects delivered with full term normal delivery. We observed that mean duration of stage I in dinoprostone group (10.6 min) was significantly lesser as compared to mifepristone group (14.2 min) (p value <0.0001). The duration of stage II was not significantly different in any of the study groups. The duration of stage III was relatively lesser in mifepristone group (4.32 min) (p-value:0.002). The induction to delivery interval was lesser in dinoprostone group (17.45 min) as compared to mifepristone group (22.8 min) (p-value: <0.0001) (Table 1)

Mode of delivery: In the current study we assessed the mode of delivery among the study subjects. We observed that majority of the study subjects were delivered with full term normal delivery (67.5% and 60% resp), whereas 27.5% and 40% study subjects resp in either groups delivered witg LSCS. The difference was not found to be statistically significant. (The chi-square statistic is 1.3976. The p-value is .237122. Not significant at p < .05.) (Table 1)
Table 1
Demographic and clinical information

<table>
<thead>
<tr>
<th>Demographic and clinical information</th>
<th>Mifeprisone (N=40)</th>
<th>Dinoprostone (N=40)</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Age distribution</td>
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<td>Less than 25 years</td>
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<td>20</td>
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<td>More than 36</td>
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<td>16</td>
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</tr>
<tr>
<td>Gravida</td>
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<tr>
<td>Primigravida</td>
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<td>25</td>
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<tr>
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<tr>
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<tr>
<td>2</td>
<td>10</td>
<td>12</td>
<td>The p-value is 0.758954</td>
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<tr>
<td>3</td>
<td>28</td>
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</tr>
<tr>
<td>4</td>
<td>2</td>
<td>3</td>
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</tr>
<tr>
<td>Bishops score (at augmentation)</td>
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<tr>
<td>Less than 6</td>
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<td>19</td>
<td>The chi-square statistic is 0.202.</td>
</tr>
<tr>
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<td></td>
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<tr>
<td>Oxytocin augmentation</td>
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<tr>
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<td>28</td>
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<td>FTND</td>
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<td>24</td>
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<tr>
<td>LSCS</td>
<td>13</td>
<td>16</td>
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</tr>
</tbody>
</table>

Indications for caesarian section: In the current study we assessed the Indications for caesarian section among the study subjects. We observed that failed induction was the commonest reason for caesarian section (25% and 27.5% among either group), followed by fetal distress among 7.5% and 10% among either study groups. (Figure 2) Mean blood loss: In the present study we assessed the mean blood loss among the study subjects. We observed that mean blood loss in Mifepristone group was 187.6 ml, whereas in dinorpstone group was comparatively greater 232.8 ml. The difference was found to be statistically significant (p value: <0.0001) (Table 2)
Neonatal complications: In the present study we assessed the neonatal complications among the study subjects. We observed that Respiratory distress, Meconium aspiration, TTN, NICU admission were comparatively found to be lesser in mifepristone group as compared to dinoprostone group. NICU admission were required more in dinoprostone group (10%), as compared to mifepristone group (7.5%). (Figure 2)
Discussion

There are various methods of induction of labor available but none of them is ideal. Various studies have been done to evaluate the role of mifepristone at term. So, the purpose of our study was to compare the efficacy of mifepristone with that of PGE2 gel. The rationale behind this study was to utilize the antiprogestrogenic activity of mifepristone at term and to find out whether it is a suitable and effective labor-inducing agent. In our study, baseline characteristics like age, booking status, socioeconomic status, education, parity, period of gestation, indication for the induction of labor, and Bishops score were comparable in both groups.

In the present study we assessed the age distribution of the study subjects. We observed that majority of the study subjects belonged to the age group of 26 to 35 years (55% and 50% in either group), followed by more than 36 years (37.5% and 40% resp). Wing et al\textsuperscript{11} in Southern California, Los Angels, conducted a randomized controlled trial in which 88 percent of the patients were in the age bracket of 21-30 years. Kanan Yelikar et al\textsuperscript{12} in their study observed that the mean age of the study subjects is 22.98 years. If we compare parity in both groups, the groups were comparable (p = 0.310). Similarly in studies done by Yellikar et al\textsuperscript{12}, mean parity was 1.48 ± 0.44 and 1.62 ± 0.44 (p= 0.659). Gupta et al\textsuperscript{13} also compared the effectiveness of mifepristone, and the groups were comparable (p <0.0310). In our study, the mean gestation age was comparable (p= 0.239). In a similar study, Sah and Padhye discovered that there was no statistically significant difference in gestational age between the two groups.

In this study we assessed the gravida status among the study subjects. We observed that majority were primigravida (72.5% and 62.5 resp).In this aspect our study correlates with studies done by Giacalone et al\textsuperscript{14}, Department of Obstetrics and Gynaecology, Hospital Arnaud de Villeneuve, University of
Montepetlier. Similar to the Wing DA et al\cite{11}, Elliot et al\cite{15} study and Kanan Yelikar\cite{12}, these trials compared mifepristone to placebo, whereas here PGE2 gel was used.

In the present study we assessed the Bishops score at the start. We observed that majority of the subjects had score of 3 (70\% and 62.5\% resp), followed by score 2 (25\% and 30\% resp). Our findings are similar to those of Elliot et al\cite{15}, Department of Obstetrics and Gynecology, University of Edinburgh, United Kingdom, 1998, who included Bishop's score of 4 or less in the research group. The mean Bishop's score at the start of our study was 2.72, which is comparable to the mean Bishop's score at the start of Kanan Yelikar's study, which was 2.02. Yelikar et al\cite{12}, and Gupta et al\cite{13} compared oral mifepristone versus placebo and found that preinduction Bishop score in both groups was 2.02 ± 0.749 and 2.79 ± 1.29, respectively. In contrast to our study, Sailatha et al\cite{16}, found that the mean increase in post-induction Bishops score at 24 hours was 4 ± 1.48 in mifepristone group and 4.7 ± 1.49 in PGE2 gel group, and this was statistically significant ($p = 0.042$).

In the present study we assessed the Bishops score at augmentation. We observed that majority of the subjects had score more than 6 (57.5\% and 52.5\% resp in both study groups). The difference between the observations in either groups was not found to be statistically significant. (The chi-square statistic is 0.202. The p-value is .653095. Not significant at $p < .05$.), which was consistent with Frydman et al study, Giacalone et al\cite{14} study, Wing DA et al\cite{11} study and Elliot et al\cite{15} study. In our study, the mean Bishop's score in the mifepristone group at the end of 24 hours was 5.68, which is comparable to Kanan Yelikar's\cite{12} study, which was 5.04. The mean rise in post-induction Bishops score after 24 hours was 6.40±1.64 in the mifepristone group and 5.26±1.85 in the dinoprostone group, according to Sah and Padhye,\cite{17} and the difference was statistically significant, $p = 0.002$. Dixit et al.\cite{18} compared the role of dinoprostone and isosorbide mononitrate and found that a change in mean Bishop score at 24 hours was statistically more in the PGE2 group than in the isosorbide mononitrate group (2.91 ± 1.34 in the IMN group and 4.52 ± 2.22 in the PGE2 group).

In the present study we assessed the need of oxytocin augmentation among the study subjects. We observed that oxytocin augmentation was required significantly more among mifepristone group (90\%), as compared to dinoprostone group (70\%). (The chi-square statistic is 5. The p-value is .025347. Significant at $p < .05$.). In this regard, our findings are similar to those of Wing DA et al,\cite{11} 2002, who found that when mifepristone was given, patients who delivered vaginally needed oxytocin for augmentation.

In the current study we assessed the duration of labour among the study subjects delivered with full term normal delivery. We observed that mean duration of stage I in dinoprostone group (10.6 min) was significantly lesser as compared to mifepristone group (14.2 min) ($p$ value <0.0001). The duration of stage II was not significantly different in any of the study groups. The duration of stage III was relatively lesser in mifepristone group (4.32 min) (p-value:0.002).
The induction to delivery interval was significantly lesser in dinoprostone group (17.45 min) as compared to midfepristone group (22.8 min) (p-value: <0.0001)

Yellikar et al.\textsuperscript{12} compared mifepristone with placebo for cervical ripening and found induction to active phase of labor 26.63 hours in mifepristone group and 29.38 hours in placebo group, and the difference was statistically significant ($p = 0.004$). Pal and Khalua\textsuperscript{19} found that induction delivery interval in mifepristone treated group (mean 28.72 ± 3.24 hours) was more than in dinoprostone-treated group (mean 10.3 ± 2.42 hours). There was statistically significant difference between the two groups as $p$-value was <0.01. In contrary to our study, Sah and Padhye\textsuperscript{17} found that induction delivery interval in mifepristone-treated group (mean 39.06 ± 15.00 hours) was less than in dinoprostone-treated group (mean 41.30 ± 17.41 hours) ($p$-value 0.493). Baev et al compared mifepristone with placebo and found that the induction delivery interval was significantly ($p$-value <0.001) less in mifepristone (2.69 ± 2.06 days) than in expectant group (3.77 ± 1.86 days).\textsuperscript{20}

In the current study we assessed the mode of delivery among the study subjects. We observed that majority of the study subjects were delivered with full term normal delivery (67.5% and 60% resp), whereas 27.5% and 40% study subjects resp in either groups delivered with LSCS. The difference was not found to be statistically significant. (The chi-square statistic is 1.3976. The p-value is .237122. Not significant at $p < .05$.) Various studied reported the incidence of FTND as follows: Giacalone et al 80.5% \textsuperscript{118} Lil et al 80.88% \textsuperscript{21} Suh et al 22.58% \textsuperscript{22} Wing DA et al 87.5% \textsuperscript{11} Gaikwad et al,\textsuperscript{23} found that the normal vaginal delivery in group A and group B was 42 (84%) and 28 (56%), while LSCS was 8 (16%) and 22 (44%), respectively. Similarly, Sah and Padhye\textsuperscript{17} discovered that in the mifepristone group, 35 (70%) patients delivered vaginally and 15 (30%) had a caesarean section. There were 34 (58%) vaginal deliveries and 16 (32%) caesarean deliveries in the dinoprostone group, although the difference was not statistically significant ($p = 0.49$). In the current study we assessed the Indications for caesarian section among the study subjects. We observed that failed induction was the commonest reason for caesarian section (25% and 27.5% among either group), followed by fetal distress among 7.5% and 10% among either study groups.

In the present study we assessed the mean blood loss among the study subjects. We observed that mean blood loss in Mifepristone group was 187.6 ml, whereas in dinoprostone group was comparatively greater 232.8 ml. The difference was found to be statistically significant (p value: <0.0001). In the present study we assessed the neonatal complications among the study subjects. We observed that Respiratory distress, Meconium aspiration, TTN, NICU admission were comparatively found to be lesser in mifepristone group as compared to dinoprostone group. NICU admission were required more in dinoprostone group (10%), as compared to mifepristone group (7.5%). Wing DA et al\textsuperscript{11} discovered that there was no statistically significant difference in neonatal outcome between the mifepristone-treated and control groups. Our findings are similar to those of Kanan Yelikar, who found no statistically significant differences in perinatal outcomes between two groups.
Sandhya Kumari et al\textsuperscript{24} in their study observed that the NNU admission was less in mifepristone group 9 (10.2%) as compared to PGE2 group 15 (16.3%) and the proportion of NNU admission in group B was relatively more than the group A but no statistically significant difference was noted (p = 0.231). Three babies in each group had an Apgar score of 6 at 5 minutes in their study, and there was no statistically significant difference between them (p= 0.956). Gaikwad et al.\textsuperscript{23} found that 6 and 14 percent of newborns in the mifepristone and dinoprostone groups, respectively, required NICU admission, which was similar to our findings. Among the babies, 36% required baby unit admission in mifepristone. In contrast to our findings, Sah and Padhye discovered that in the mifepristone group, 5 (10%) neonates required NICU admission while in the dinoprostone group, 1 (2%) babies required NICU admission. There was no significant association in NICU admission (p = 0.069) among two groups.

**Conclusions**

Oral mifepristone is a very safe and effective treatment for preinduction cervical ripening, according to this study. It offers the advantages of being simple to administer, higher patient compliance and acceptability. This study shows shorter labour stages I and III, and less blood loss in mifepristone group.

The drug has no significant effects on uterine contraction and no serious maternal complications. This drug has a safe neonatal outcome. Patient can remain ambulatory, which is very convenient as compared to PGE2 gel. PgE2 gel needs refrigerator for storage and skill for intracervical insertion with strict aseptic technique. Hence mifepristone offers advantages over PGE2 gel which is currently used for preinduction cervical ripening.

**Conflict Of Interest: none to declare**

**References**