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Original Article

A Clinical Evaluation of Mifepristone as a Cervical Ripening Agent and Labour Inducer in Term Pregnancies

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Abstract

Background: To evaluate the efficacy of mifepristone in pre induction cervical ripening in term pregnancy. ***Materials and Methods:*** Prospective interventional randomised comparative study, done at Holy family hospital New Delhi. 100 patients were selected randomly with a bishop score less than 6. The study group included fifty patients who received 200 mg oral mifepristone (if applicable, repeat once after 24 hrs). The expectant group included 50 patients, whom we observed for 48hrs without interference. Comparison was done in terms of improvement in bishop score, need for further induction and augmentation of labour, induction to delivery interval and mode of delivery. ***Results:*** In the mifepristone group, there was a statistically significant difference in the number of PGE2 gel required with a p value of 0.0001. The study group demonstrated a significantly lower proportion of patients requiring further doses of PGE2 gel compared to the expectant group. The median PGE2 gel to delivery interval in the expectant group was 11.5hrs which was significantly higher compared to the study group, where the median interval was 8 hrs. In our study there was a statistically insignificant difference in the improvement in the bishop score with a p-value of 0.824, also in terms of complications and neonatal outcome. ***Conclusion:*** This study showed that oral mifepristone given for pre induction cervical ripening is an effective agent when given at least 24- 48 hrs prior in full term pregnancy.

Keywords: ***Mifepristone; Induction of labor; Modified bishop score; cervical ripening; Term pregnancy; Cesarean section.***

Introduction

Induction of labor is intervention done artificially to initiate the process of labor in a quiescent uterus leading to progressive dilatation & effacement of cervix. A favorable cervix, characterized by dilatation and effacement, increases the likelihood of a successful induction of labor. When delivery is necessary, and ripening has not had time to occur this natural process has to be accelerated [1]. All unfavorable or unripe cervix (with a Bishop score of<6) need an agent to first ripen the cervix before the induction is to be considered [2]. As it is a 19 nor steroid which has a greater affinity for progesterone receptors than does progesterone itself, it blocks the action of progesterone at the cellular level. It antagonizes progesterone and thus increases sensitivity of the uterus to prostaglandins and initiates labor [3]. Mifepristone is absorbed rapidly after oral administration, reaching maximum serum level within 2 hrs. And has a half-life of about 25 hrs [4].

Materials & Methods

This was a prospective interventional randomised comparative study. The study was carried out in the department of the obstetrics and gynecology of Holy family hospital, New Delhi from February 2023 to January 2024.

Aim

To evaluate the efficacy and success rate of mifepristone in pre-induction ripening of the cervix in term pregnancy.

Objectives

To study the proportion of patients with a modified bishop score >= 6 at the end of 24 hrs. Need for induction / augmentation of labor.

1. To study induction delivery interval
2. Maternal and fetal outcome

Maternal outcome
Mode of delivery

- Normal vaginal delivery
- LSCS in view of failed induction
- Instrumental delivery

Adverse drug effect
Maternal Complications: cervical tear, hematoma, uterine rupture

FETAL OUTCOME: Apgar score, Meconium aspiration syndrome, Fetal distress, NICU admission

Inclusion Criteria

1. Singleton, term, live pregnancies with a cephalic presentation & a cervical Bishop score of less than 6 were included in the study group.
2. Induction could be deferred for 24 hrs
3. Intact membranes

Including both high and low risk pregnancies.

Exclusion Criteria

1. Parity greater than 3
2. Malpresentation
3. Previous Cesarean / hysterotomy • Cephalopelvic Disproportion
4. Antepartum Hemorrhage
5. Pelvic tumors
6. Multiple Pregnancy
7. Placenta previa
8. Intrauterine death of fetus
9. Cervical fibroid

Block Randomization

Block Randomization with Sealed envelope system: In this, I will prepare ten sealed opaque envelopes assigning A and B in 5 envelopes each, where one label represents study group and other label represents expectant group. Once a patient will consent to enter a trial an envelope will be opened, and the patient will then be offered the allocated group. In this technique, patients will be randomized in a series of blocks of ten.

Method of Data Collection

Our study was conducted at Holy Family Hospital, New Delhi. A detailed history including general and obstetric examination was done. A modified Bishop score was calculated, following a vaginal examination. Patients were recruited in the study after informed consent obtained from them.100 patients were selected randomly with Bishop score < 6, 50 patients who received oral mifepristone 200 mg for preinduction cervical ripening were included in the study group and other 50 women in whom we did not have any intervention for cervical ripening were included in the expectant group.

Study Group

The study group participants, with a modified Bishop score of less than 6, were given the first dose of tablet mifepristone 200 mg orally. Modified Bishop score was reassessed after 24 hrs. of the first dose of tablet mifepristone 200 mg. At the end of 24 hrs. if a modified Bishop score was more than 6, intracervical prostaglandin (PGE2) gel was kept every six hours (maximum 3 doses). At the end of 24 hrs. if a modified Bishop score was < 6, the second dose of tablet mifepristone 200 mg was given orally and a modified Bishop score was reassessed after 24 hrs. of the second dose of tablet mifepristone. Induction was done with PGE2 gel at the end of two doses of mifepristone irrespective of the modified Bishop score or after one dose of mifepristone if there was a good change in the modified Bishop score. Artificially rupture of membranes and oxytocin augmentation was done if necessary.

Expectant Group

The expectant group participants with a modified Bishop score of less than 6 were observed for a period of 48 hrs without any intervention for any spontaneous change in the modified Bishop score. Following 48 Hrs of inactivity, they were induced with PGE2 gel six hourly (maximum 3 doses). Artificial rupture of membranes and oxytocin augmentation was done if necessary.

Statistical Analysis

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the means ± SD and as median with 25th and 75th percentiles (interquartile range). The data normality was checked by using the Shapiro-Wilk test. The cases in which the data was not normal, we used nonparametric tests. The following statistical tests were applied for the results:

- The comparison of the variables which were quantitative and not normally distributed in nature were analyzed using Mann-Whitney Test and variables which were quantitative and normally distributed in nature were analyzed using independent t test.
- The comparison of the variables which were qualitative in nature were analyzed using the Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used.

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0. For statistical significance, p value of less than 0.05 was considered statistically significant

Results and observations

The study was conducted in the department of the obstetrics and gynecology of Holy Family hospital, New Delhi. 100 singleton, term, live pregnancies with a cephalic presentation & a cervical Bishop score of less than 6 were included in the study. Patients were randomly divided into two groups:

Study group (n=50): Patients received oral mifepristone 200 mg for preinduction cervical ripening.

Expectant group (n=50): No intervention was done for cervical ripening.

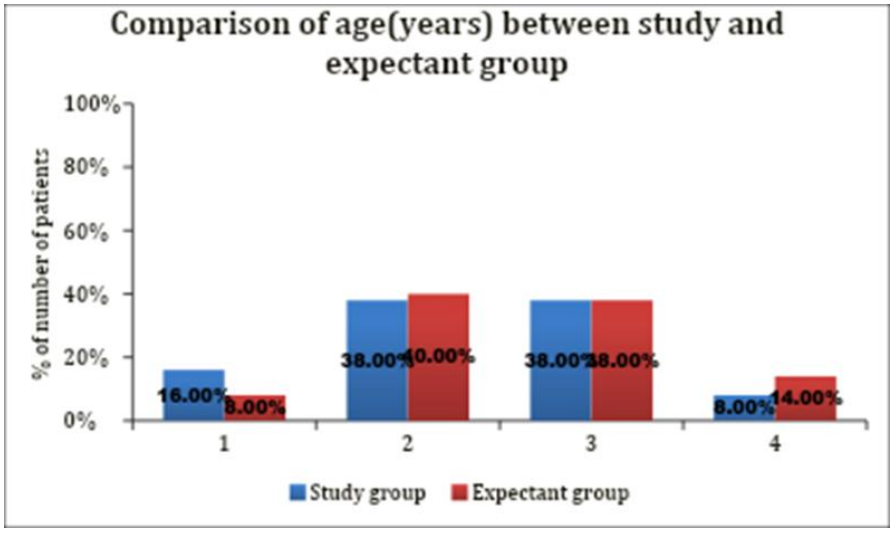

Figure 1: Comparison of age(years) between study and expectant group.

The distribution of age in both the study and expectant groups demonstrated comparability. Specifically, within the age brackets of 19-25 years, 26-30 years, 31-35 years, and >35 years, the respective percentages were as follows: 16% vs. 8%, 38% vs. 40%, 38% vs. 38%, and 8% vs. 14%. The statistical analysis, represented by a p-value of 0.536, supported this observed similarity.

Table 1: Comparison of gestational age(weeks) between study and expectant group.

Gestational age(weeks)	Study group(n=50)	Expectant group(n=50)	Total	P value
37 to 38 weeks	18 (36%)	26 (52%)	44 (44%)	0.253†
38 weeks +1 day to 39 weeks	15 (30%)	10 (20%)	25 (25%)	
39 weeks + 1 day to 40 weeks	17 (34%)	14 (28%)	31 (31%)	
Mean ± SD	38.48 ± 0.91	38.26 ± 0.97	38.37 ± 0.94	0.244‡
Median (25th-75th percentile)	38.79 (37.571-39.286)	38 (37.429-39.143)	38.43 (37.429-39.143)	
Range	37-39.86	37-40	37-40	

‡ Independent t test, † Chi square test

There was no statistical significant difference in the mean age and mean gestational age between the study and expectant groups with p value of 0.271 and 0.244 respectively. (Figure 1 and Table 1)

Table 2: Comparison of Primi/Multigravida between study and expectant group.

Primi/Multigravida	Study group(n=50)	Expectant group(n=50)	Total	P value
Primigravida	30 (60%)	24 (48%)	54 (54%)	0.229†
Multigravida	20 (40%)	26 (52%)	46 (46%)	
Total	50 (100%)	50 (100%)	100 (100%)	

† Chi square test

Table 3: Comparison of bishop score between study and expectant group.

Bishop score	Study group	Expectant group	Total	P value
At 0 hour				
Mean ± SD	2.24 ± 1.1	1.94 ± 1.02	2.09 ± 1.06	0.242§
Median (25th-75th percentile)	2(2-3)	2(2-3)	2(2-3)	
Range	0-4	0-4	0-4	
At 24 hours				
<6	21 (42%)	29 (58%)	50 (50%)	0.0003†
>=6	15 (30%)	21 (42%)	36 (36%)	
Improved and delivered	14 (28%)	0 (0%)	14 (14%)	
Mean ± SD	4.72 ± 1.77	4.58 ± 2.06	4.64 ± 1.93	0.824§
Median(25th-75th percentile)	4.5(3-6)	4(3-7)	4(3-7)	
Range	2-7	1-7	1-7	
At 48 hours				
<6	8 (38.10%)	16 (55.17%)	24 (48%)	0.241†
>=6	5 (23.81%)	8 (27.59%)	13 (26%)	
Improved and delivered	8 (38.10%)	5 (17.24%)	13 (26%)	
Mean ± SD	4.77 ± 1.88	4.5 ± 1.93	4.59 ± 1.89	0.744§
Median (25th-75th percentile)	5(3-7)	4(3-7)	4(3-7)	
Range	2-7	1-7	1-7	

§ Mann Whitney test, † Chi square test

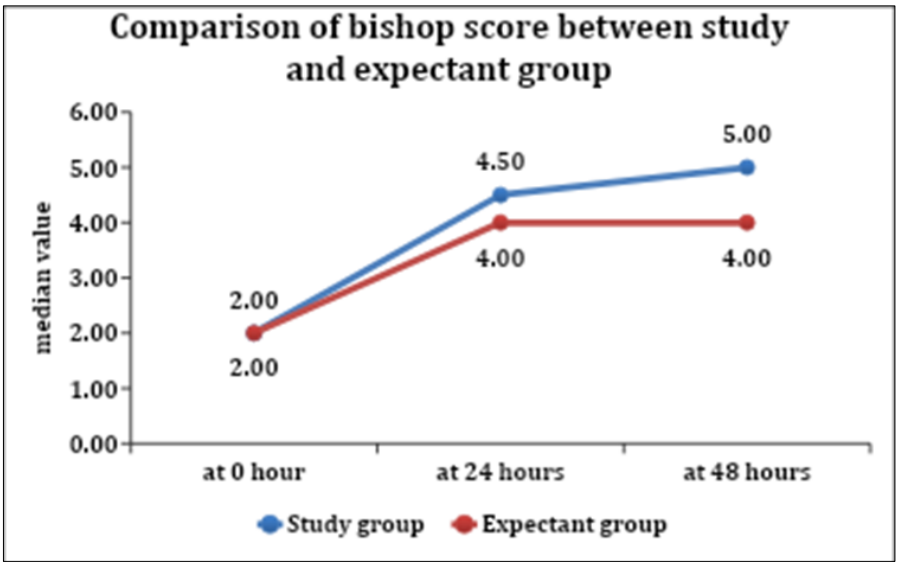

Figure 2: Comparison of trend of bishop score at different time intervals between study and expectant group.

At 0 hours, the median Bishop score (25th-75th percentile) was comparable between the study group (2, 2-3) and expectant group (2, 2-3), with a p-value of 0.242. At 24 hours, a significant difference was observed in Bishop scores below 6, with 42% in the study group compared to 58% in the expectant group (p=0.0003). Bishop scores of >=6 were 30% in the study group and 42% in the expectant group, while 28% in the study group showed improvement and delivered, as opposed to none in the expectant group. At 48 hours, Bishop scores below 6 were 38.10% in the study group and 55.17% in the expectant group (p=0.241), while scores of >=6 were 23.81% and 27.59%, respectively. Additionally, 38.10% in the study group improved and delivered, compared to 17.24% in the expectant group. Overall, these findings suggest significant differences in Bishop scores below 6 at 24 hours, indicating potential predictive value for the need for induction, while other comparisons did not reach statistical significance. (**Table 3, Figure 2**)

Table 4: Comparison of number of PGE2 gel required between study and expectant group.

Number of PGE2 gel required	Study group(n=50)	Expectant group(n=50)	Total	P value
0	29 (58%)	8 (16%)	37 (37%)	0.0001†
1	13 (26%)	19 (38%)	32 (32%)	
2	3 (6%)	12 (24%)	15 (15%)	
3	5 (10%)	11 (22%)	16 (16%)	
Total	50 (100%)	50 (100%)	100 (100%)	

† *Chi square test*

These differences in PGE2 gel requirements were statistically significant, as indicated by a p-value of 0.0001. (Table 4)

Table 5: Comparison of augmentation details between study and expectant group.

Augmentation details	Study group(n=50)	Expectant group(n=50)	Total	P value
Oxytocin	8 (16%)	14 (28%)	22 (22%)	0.148†
ARM	10 (20%)	5 (10%)	15 (15%)	0.161†
Both	6 (12%)	10 (20%)	16 (16%)	0.275†

† Chi square test

Table 6: Comparison of indication for LSCS between study and expectant group.

Indication for LSCS	Study group(n=4)	Expectant group(n=7)	Total	P value
Failed induction	1 (25%)	1 (14.29%)	2 (18.18%)	0.364*
Fetal distress + MSL	1 (25%)	0 (0%)	1 (9.09%)	
Fetal distress	0 (0%)	3 (42.86%)	3 (27.27%)	
NPOL	2 (50%)	3 (42.86%)	5 (45.45%)	
Total	4 (100%)	7 (100%)	11 (100%)	

** Fisher's exact test*

The calculated p-value of 0.364 supported the conclusion that there were no statistically significant differences in the distribution of indications for LSCS between the two groups. (Table 6)

Table 7: Comparison of maternal complication between study and expectant group.

Maternal complication	Study group(n=50)	Expectant group(n=50)	Total	P value
Nil	43 (86%)	49 (98%)	92 (92%)	0.019*
Mild PPH	0 (0%)	1 (2%)	1 (1%)	
MRP	2 (4%)	0 (0%)	2 (2%)	

Nausea	1 (2%)	0 (0%)	1 (1%)	
Vomiting	4 (8%)	0 (0%)	4 (4%)	
Total	50 (100%)	50 (100%)	100 (100%)	

** Fisher's exact test*

Comparison of fetal complication between study and expectant group. * Fisher's exact test, † Chi square test

The study did not identify statistically significant differences in fetal complications and birth weight between the study and expectant groups.

The mean APGAR score at 1 minute ± standard deviation for the study group was 8 ± 0.78, while in the expectant group, it was 8.12 ± 1, and the overall mean across both groups was 8.06 ± 0.9, with a non-significant p-value of 0.506.

At 5 minutes, all infants in both groups had APGAR scores of 7 or higher, totaling 100%. The mean APGAR score ± standard deviation for the study group was 9.32 ± 0.62, and for the expectant group, it was 9.1 ± 0.65. The overall mean across both groups was 9.21 ± 0.64, with a non-significant p-value of 0.086.

Comparison of NICU admission between study and expectant group.

The calculated p-value of 0.161 indicated no statistically significant differences in the distribution of NICU admission between the two groups, suggesting a similar pattern of neonatal care needs in both study and expectant groups.

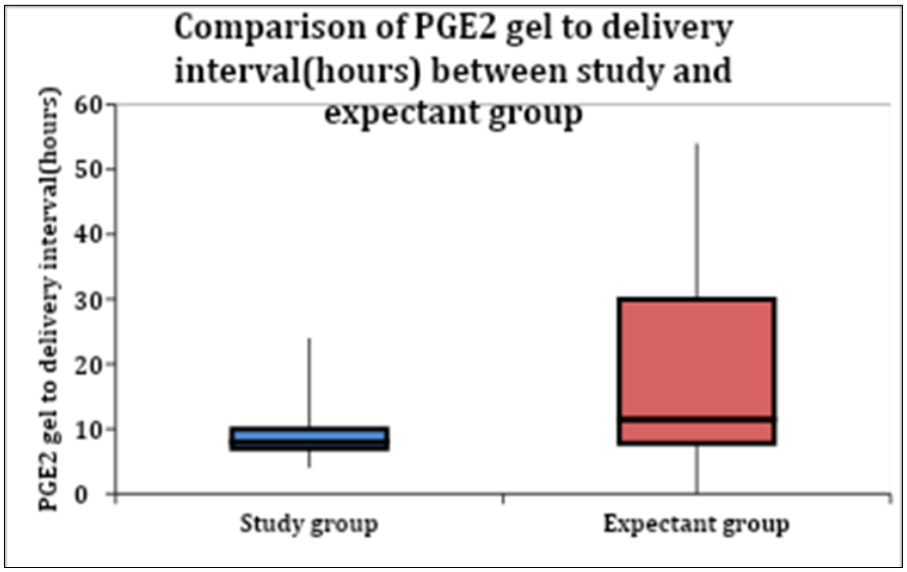

Figure 3: Comparison of PGE2 gel to delivery interval(hours) between study and expectant group. (non-parametric variable, Box-whisker plot)

The median PGE2 gel-to-delivery interval in the expectant group was 11.5 hours (25th-75th percentile: 7.75-30), and this duration was significantly higher compared to the study group, where the median interval was 8 hours (25th-75th percentile: 7-10) (p=0.036). This finding suggests a statistically significant difference in the time it took for delivery to occur after the administration of PGE2 gel between the two groups, with a longer interval observed in the expectant group (Figure 3).

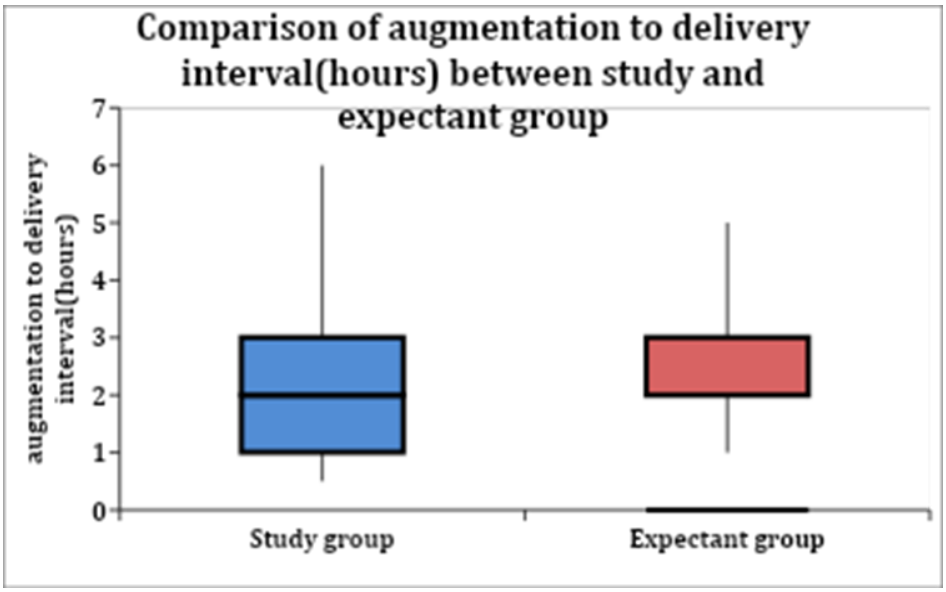

Figure 4: Comparison of augmentation to delivery interval(hours) between study and expectant group. (non-parametric variable, Box-whisker plot)

There was no significant difference in the augmentation-to-delivery intervals between the two groups, as indicated by a p-value of 0.299 (Figure 4).

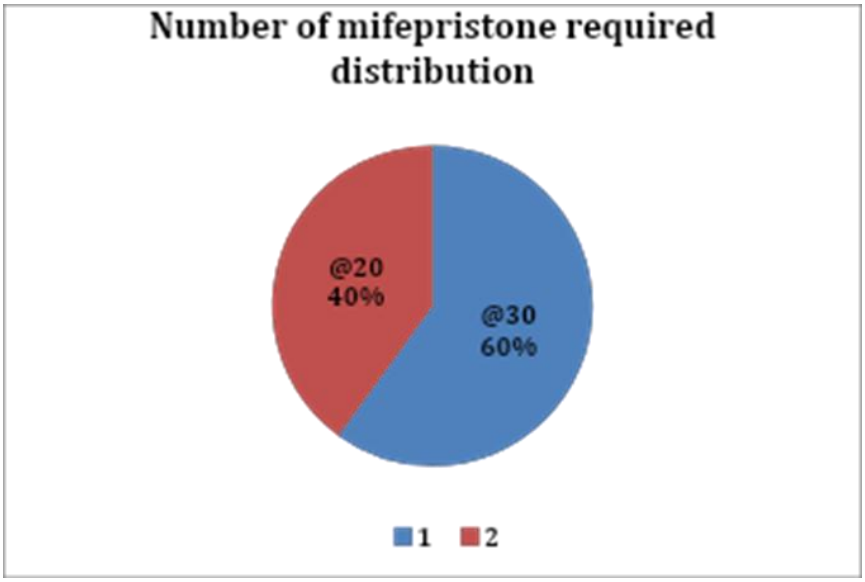

Figure 5: Number of mifepristone required distribution.

Out of a total of 50 cases, 60% (30 cases) required one dose of Mife, while 40% (20 cases) required two doses. (Figure 5)

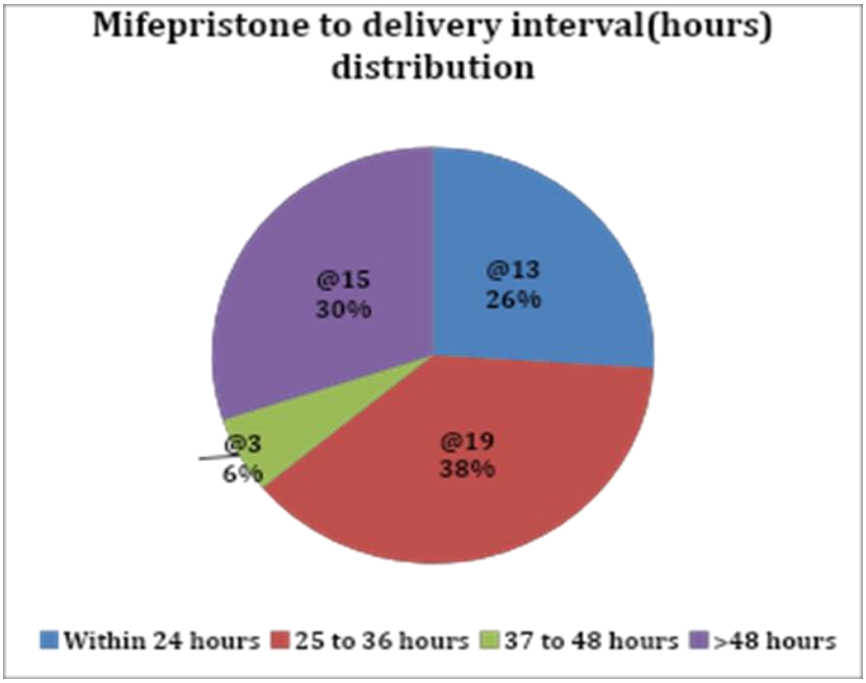

Figure 6: Mifepristone to delivery interval(hours) distribution.

Among the study subjects, the Mifepristone to delivery interval varied, with 38.00% (19 cases) experiencing a duration of 25 to 36 hours, 30.00% (15 cases) exceeding 48 hours, 26.00% (13 cases) occurring within 24 hours, and 6.00% (3 cases) falling between 37 to 48 hours. The mean Mifepristone to delivery interval for the study subjects was 37.38 ± 19.4 hours, with a median (25th-75th percentile) of 32 hours (24.5-54) (Figure 6).

Discussion

The study was conducted at Holy Family Hospital, NEW DELHI. The study and the expectant group, each had 50 participants. In our study, at admission there were no statistically significant differences in age, parity, gestational age or modified bishop score between the study and the expectant group. The maximum patients were in the age group 26 yrs to 35 yrs.

- In our study group, 200 mg of mifepristone was given when the modified bishop score was less than 6. If after 24hrs, the modified bishop score improved then the patient was induced with intracervical dinoprostone gel installation.

After 24 hrs if the modified bishop score remained <= 6 then 200 mg of mifepristone was repeated which is similar to Frydman *et al.*[5] and Oleg *et al.*[6] study. After 24 hrs of the second dose of mifepristone irrespective of the modified bishop score, the patient was induced with intracervical dinoprostone gel done if necessary. The expectant group participants were observed for 48 hrs without any intervention. There was no statistically significant improvement in the change of bishop score among the study group and the expectant group.

This was not comparable to the study done by Sujithra S *et al.*[7] and Li *et al.*[8] who observed 100 % cervical ripening rate at the end of 48 hrs of tablet mifepristone.

In the present study, out of 50 patients, 29 (58%) patients did not require any PGE2 gel. 13 (26%), 3(6%) and 5 (10%) patients required 1, 2 and 3 PGE2 gel respectively. Whereas in the expectant group only 8 (16%) patients delivered without the need of PGE2 gel. 19 (38%), 12 (24%) and 11 (22%) patients required 1, 2 and 3 PGE2 gel respectively. There was a statistically significant difference in the number of PGE2 gel required between the study and the expectant group with a p value of 0.0001. Wing *et al.*[9] and Yelikar *et al.*[10] also observed the reduced need for further inducing agent after the cervical ripening being done by tablet mifepristone.

In our study, 14 (28%) patients delivered spontaneously within 24 hrs of the tablet mifepristone, and they did not require any further inducing agent. So in total out of 50 patients in the study group, 29 (58%) patients did not require any further inducing agent (PGE2 gel). ARM and oxytocin were done, if necessary. Oleg *et al.*[6] also observed that 20% went into spontaneous vaginal delivery within 24 hrs of mifepristone. In the study done by Sujithra S7 *et al.* observed that significantly less number of PGE2 gel were required in the study group.

In the present study, out of 50 participants 8 (16%) required oxytocin, 10 (20%) required ARM and 6 (12%) required both oxytocin and ARM as an augmentation in the study group. In the expectant group 14 (28%) , 5 (10%) and 10 (20%) participants required oxytocin, ARM and both respectively. Statistically there was no significant decrease in the need for augmentation among the two groups. Though clinically there was significant reduction in the need of augmentation after the use of oral mifepristone. In our study, there was statistically no significant difference in the mode of delivery. In the study group, out of 50 patients, 43 delivered vaginally, 3 were instrumental delivery, 4 were LSCS.

In terms of maternal complications, the mifepristone group had 2 cases with manual removal of placenta and no case of PPH. In the expectant group there was 1 case of PPH. In the mifepristone group, 1 patient had nausea and 4 patients had vomiting. In our study out of a total 50 patients, 43 (86%) had no fetal complications. 4 had neonatal jaundice, 3 had fetal distress. There was no significant difference in the mean birth weight between the study and the expectant group, as reflected by p value of 0.37. In our study, both groups had 2 patients with an Apgar score less than 7 at 1 min. None of the patients had an Apgar score less than 7 at 5 minutes. These findings indicate a similar APGAR score in the study and the expectant group.

There was no statistical significant difference in the two groups in terms of neonatal admission. Even in the study done by Sujithra S *et al.*[7] respiratory distress was equal in both the groups (2%).

In our study time taken from PGE2 gel to delivery interval was lesser in the mifepristone group as compared to the expectant group. The median PGE2 gel to delivery interval was 11.5 hrs in the expectant group and 8 hrs in the study group. This finding suggests a statistical significant difference in the time it took for delivery to occur after the administration of PGE2 gel between the two groups, with a longer interval observed in the expectant group. In the study done by Yelikar *et al.*[10] there was significant reduction in duration from induction to delivery interval in the study group compared to the control group. Similar results were reported by wing *et al.*[9] and Hapangama and Neilson3. Sujithra S *et al.*[7] and Wing *et al.*[9] also observed a shorter induction to delivery interval in the study group compared to the control group.

In our study, out of 50 patients in the study group, 60% (30 cases) required one dose of mifepristone, while 40% (20 cases) required two doses. Out of 50 patients, 14 (28%) patients had improvement in bishop score and delivered within 24 hrs of the first dose of mifepristone. Whereas in the expectant group, 50 patients none of the patients delivered within 24 hrs. Only 21 (42%) patients required a second dose of mifepristone, out of which 8 (38.10%) patients improved and delivered vaginally within the next 24 hrs.

Conclusion

This present study showed that oral mifepristone given for preinduction cervical ripening is an effective induction agent when given at least 24-48 hrs prior in full term pregnancies. The mifepristone acts as an alternative inducing agent which is a safe, effective, convenient cervical ripening agent with no serious maternal or neonatal outcome and with reduced PGE2 gel to delivery interval.

Declarations

Funding

No funding sources.

Conflict of interest

None declared.

Ethical approval

Done

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