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Indian Journal of Obstetrics and Gynecology Research

Journal homepage: www.ijogr.org

Original Research Article

Comparative analysis of safety, efficacy and fetomaternal outcome of cervical priming with mifepristone versus intracervical dinoprostone gel

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ARTICLE INFO

Article history:
Received 24-01-2024
Accepted 26-07-2024
Available online 15-02-2025

Keywords:
Cervical priming
Preinduction ripening
Dinoprostone gel

ABSTRACT

Aim: The aim of this study was to evaluate the efficacy and safety of mifepristone forcervical ripening and induction of labor and compare the results with dinoprostone gelwhich is an established agent for labor induction.

Materials and Methods: A total of 200 patients were enrolled in a prospective study and 100 eachwere assigned to either Mifepristone (M) Group and Dinoprostone (D) group. Outcome was evaluated using the improvement in Bishop score (BS), admission delivery interval, duration between induction and the onset of active phase of labor, mode of delivery and maternal and fatal outcomes.

Results: Though not statistically significant a single dose of 200mg Mifepristone resulted in better BS at 48hrs post application. The M group required lesser doses of Dinoprostone gel for labour induction and had lesser LSCS rates. The Apgar scores at1 and 5 mins were significantly better in M group.

Conclusion: The results of the study suggest that oral administration of 200mg mifepristone in term patients is more efficacious than Dinoprostone gel for cervical priming by achieving a better BS at 48 hrs. There is a significant reduction in application to delivery time and a significant reduction in LSCS rates.

1. Introduction

In an unflawed world, all women would endure spontaneous onset of labour pains, terminating in a normal vaginal delivery with no intervention. But this picture is anything but idyllic. Up to 20% of women worldwide undergo induction of labor for a variety of causes and by one or the other available methods.[1] In 1997, the World Health Organization defined normal birth as "spontaneous in onset with the infant born in the vertex position at term with low risk to mother and baby throughout labour resulting in a healthy mother and infant."[2,3] The model method for labour induction would simulate the process of onset of spontaneous labour unerringly. It often becomes essential to induce labour when the benefits of continuing the pregnancy become marginal to either the mother or the fetus.

The Society of Obstetricians & Gynaecologists in Canada states that induction of nulliparas is associated with twice the chance of caesarean birth as compared with spontaneous labour.[2] ACOG suggests that labour may be induced for logistic reasons, including the risk of rapid delivery, distance from the hospital and psychological reasons.[4]

Cervical ripening and initiation of uterine contractions are two key constituents of labour induction. From prostaglandin analogues to mechanical procedures like insertion of the transcervical catheter, membrane stripping, application of hygroscopic cervical dilators, etc have been used for cervical ripening for decades.[3]

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https://doi.org/10.18231/j.ijogr.2025.023

A 19 nor-steroid anti-progestin drug -Mifepristone blocks the progesterone receptors at the cellular level. Consequentially it leads to decidual necrosis, vascular impairment, and bleeding. The falling progesterone levels subsequently lead to the onset of labor. Innumerable studies have shown the efficacy of mifepristone as a successful cervical priming agent. Apart from softening the cervix and increasing the sensitivity to prostaglandins, it converts the quiescent pregnant uterus into an active organ.[5] In comparison, dinoprostone, is a conventionally used naturally occurring prostaglandin E2 (PG E2) which by its ability to cause collagen lysis causes cervical ripening along with its oxytocin-like effect on pregnant uterus.[4]

2. Materials and Methods

This was a prospective comparative study done at a tertiary level hospital to evaluate the efficacy and safety of oral Mifepristone vs intracervical Dinoprostone gel for cervical priming of pregnant women at term for 02yrs from 2017 to 2019. 200 such women were randomly allocated into 02 groups – Mifepristone (M) and Dinoprostone (D) group of 100 each. (Figure 1)

The objective of the study was to study the safety and efficacy of mifepristone for cervical priming, to compare the effect of mifepristone in a study group with that of dinoprostone in the improvement of Bishop Score, to study the necessity for augmentation of labour and induction to the delivery period between the two groups and to discern the maternal and neonatal outcomes in both groups.

2.1. Study design

The inclusion criteria of the study consisted of (i) Consenting patients (ii) Singleton, primigravid, and multigravida (< 3) pregnancy (iii) Pregnancy at or > 40 weeks POG (iv) Cephalic presentation (v) Non scarred uterus (vi) Normal NST and USG at term (vii) Bishop score less than 6.

2.2. Methodology

After admission detailed patient history was taken and a complete general and systemic examination was done. All dates were confirmed with ultrasounds. Under aseptic precaution per vaginal examination was done and pelvic assessment was carried out. Bishop's score was documented. Ultrasonography was done in the labour room to confirm the fetal position, liquor, and placental localization. An Admission Non-Stress Test (NST) was done and an indication for termination of pregnancy was recorded.

Written and informed consent was taken from all women willing to undergo cervical ripening agents. Adequate couple counseling was done before the procedure after explaining all the merits and adverse effects. All guidelines as per the declaration of Helsinki and good clinical practice guidelines were followed. Women were asked to pick randomly, papers marked M (Mifepristone group) or D (Dinoprostone group) in the labor room. 100 women were studied in each group. Bishop's score was documented pre-application of the ripening agent.

M Group: 100 women were given 200 mg T Mifepristone per orally on day 1.

D Group: 100 women were administered 0 2mg intracervical dinoprostone gel on day 1.

Women in both groups were observed for 1hr post-application in the labour room with continuous NST monitoring. After 24 hours & 48 hours per vaginum examination was repeated and the Bishop score was documented. If Bishop score was ≥ 6, membranes ruptured or if the patient developed uterine contractions, labour was augmented with titrated oxytocin regimens. Labour was monitored with partogram and CTG monitoring.

However, if after 48hrs Bishop's score remained < 6, dinoprostone gel was applied for induction of labour, and the case was documented as Mifepristone failure for the M group. In the D group, if after 48hrs Bishop's score remained < 6, 3 more doses of dinoprostone gel were applied 6 hrly for induction of labour.

2.3. Statistical analysis

The entire data was analyzed using Statistical Package for Social Sciences (SPSS ver 21.0, IBM Corporation, USA) for Mac. In the study, the p-values less than 0.05 were taken as statistically significant. The data on categorical variables has been shown as N (% of cases) and mean with standard deviation (SD). For inter-group comparison of the distribution of categorical variables, Chi-Square test was used. Fisher's exact probability test for a 2 x 2 contingency table was used for univariate analysis. Multivariate odds along with 95% CI of odds have been provided in the logistic regression analysis.

3. Results

The patient consort flowchart (Figure 2) shows the enrollment, allocation, follow, and analysis of patients in the study. There were no significant statistical differences between the age distribution of the two groups. The mean age was 27.18 years and the standard deviation was 3.614 years. The incidence of primigravidas was 64 (64%) in the M group and 72 (72%) in the D group.

The mean Bishop score (BS) at inclusion was 3.1 in the M group and 3 in the D group. (Table 1) There was no significant difference in pre-induction BS in the two groups. Post-induction change in BS in the M group was 7.12 (± 1.63) and G group 6.5 (± 1.51) at 48hrs with p=0.004. Though not statistically significant, a single dose of Mifepristone 200mg resulted in better BS at 48 hours

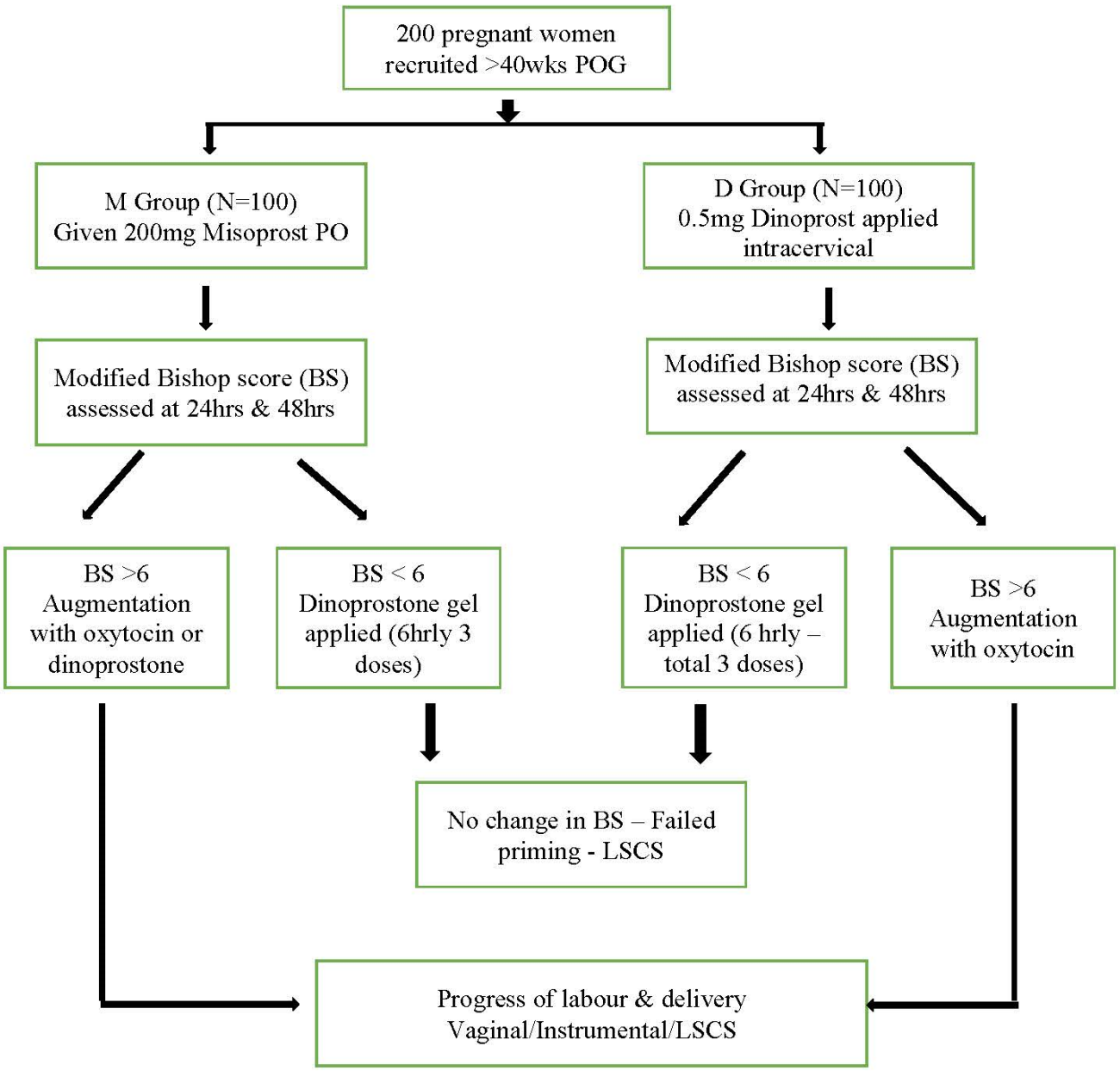

Figure 1: Study design

Table 1: Change in Mean Bishop Score at 24hrs & 48hrs in the study groups

	Mifepristone (M) Group	Dinoprostone (D) Group	p Value
Pre induction Mean Bishop score, mean (±SD)	3.1(±0.52)	3.02(±0.36)	0.103
Change in Mean Bishop score after 24 hours mean (±SD)	4.80 (± 1.32)	5.2(± 1.40)	0.02
Change in Mean Bishop score after 48 hours mean (±SD)	7.12 (± 1.63)	6.5(± 1.51)	0.004

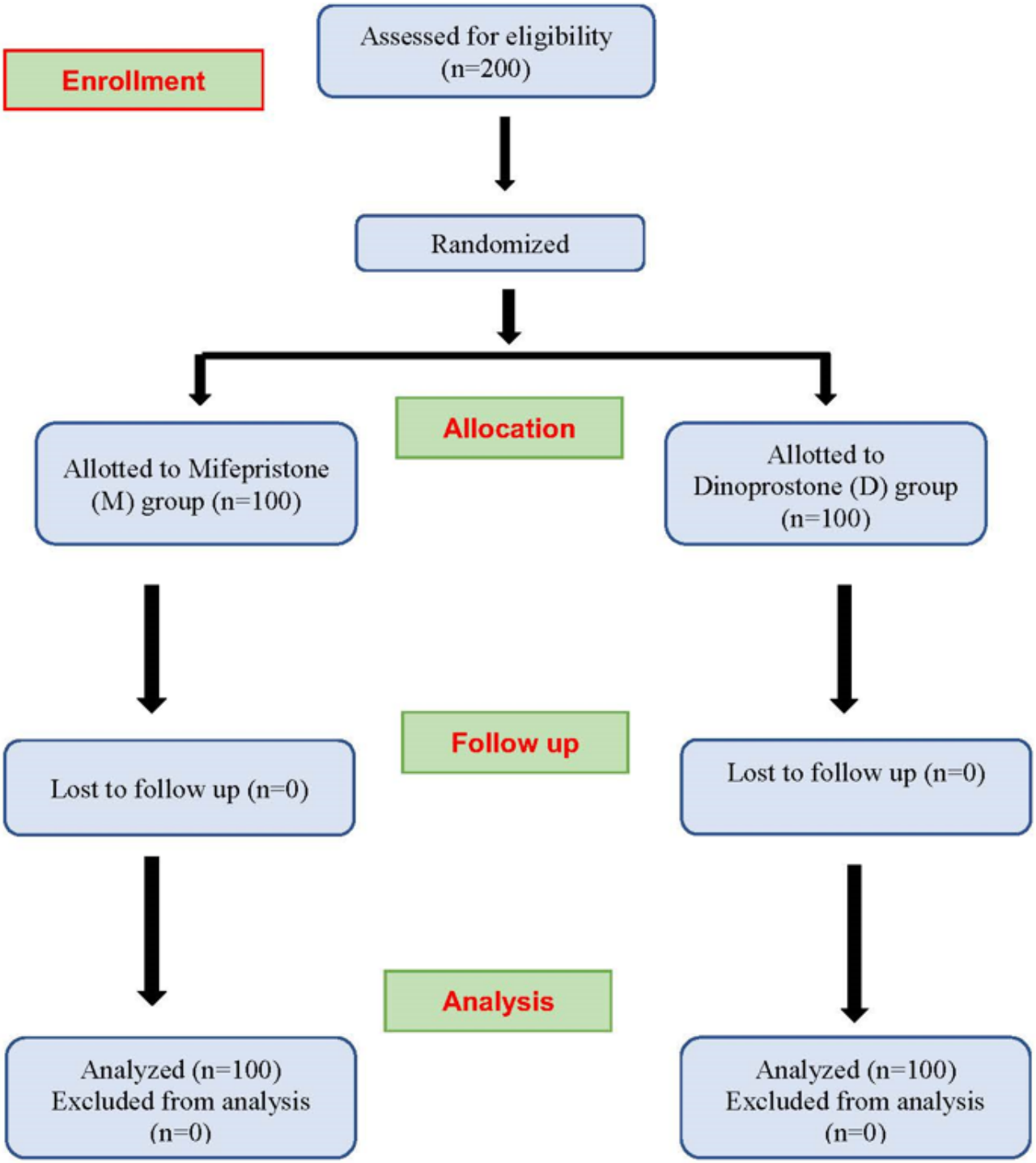

Figure 2: Patient consort flowchart

compared to 0.2mg intracervical dinoprostone.

Successful priming was taken as an improvement of Bishop score ≥6 after 48 hours of intake of mifepristone in the mifepristone group and 48 hours after the first dose of dinoprostone in the dinoprostone group. (Table 2) The success rate was 78% in the mifepristone group and 57% in the dinoprostone group. This difference was statistically significant (<0.001).

Table 2: Outcome of priming in the two groups

	Mifepristone (M) Group (N=100)	**Dinoprostone (D) Group (N=100)**	**p Value**
Successful Priming	78 (78%)	57(57%)	
Unsuccessful Priming	22(22%)	43(43%)	< 0.001

In our study, the mean duration from priming to the onset of labour pains was 28.14(±14) hrs in the M group and 35.11 (±12.3) hrs in the D group. Though women progressed to the first stage of labour earlier in the M group the difference was not statistically significant (p = 0.126). The mean priming to delivery time in the M group was 37.02(±16) hrs compared to 43(±19.2) hrs in the D group. (Table 3) Though women with mifepristone priming delivered almost 6 hours earlier than the dinoprostone group, it was statistically not significant (p=0.133).

Labour augmentation was needed in (78) 39% of women in our study with oxytocin. The requirement in the M group was 40(40%) compared to 38(38%) in the D group. The women whose BS remained unfavorable (6-8) after 48 hours were induced with dinoprostone intracervical doses at 6 hrly intervals in both groups. 22(22%) women in the M group and 43 (43%) in the D group needed dinoprostone gels. A total of 65 (32.5%) women required further dinoprostone application (mostly in the D group) to achieve a favorable BS for oxytocin augmentation and delivery. With the student T test giving a Chi-square value of 54.604, and p-value <0.001, this result was statistically significant. Analysis of the number of doses of dinoprostone required for augmentation of labour showed that the M group needed 1 mean dose compared to 2.2 in the D group. Thus, among the subjects who needed further augmentation with Dinoprostone gel, subjects in the M group needed fewer doses than subjects in the D group and this difference was statistically significant. (Table 4) Hence the use of oral Mifepristone greatly reduces not only the need for cervical priming with Dinoprostone gel but also the required number of doses.

In our study 153 (76.5%) women underwent vaginal delivery, 4 (2%) needed outlet forceps, 8(4%) required ventouse application and 35 (17.5%) needed LSCS for fetal delivery. 13(13%) women in M group underwent LSCS compared to 22(22%) in D group. Fewer subjects in the mifepristone group needed LSCS, making the difference in type of delivery statistically significant. (Table 5) The indications for LSCS varied from failed induction (25%), fetal distress (41.6%) to non-progress of labour (33.3%). Failed induction was lesser in the M group (14.2%) compared to the D group (31.8%). Fetal distress was noted in 50% of women in the M group undergoing LSCS compared to 36% in the D group. The difference was however statistically not significant (p>0.05).

Analysis of 1- and 5-min Apgar scores in our study showed mean Apgar at 1min in the M group as 5.46 compared to 4.92 in the D group (p=0.004). The mean Apgar at 5 min in the D group was 7.38 compared to 6.92 in the D group (p=0.003). At 1 minute and 5 minutes babies born to the subjects in the M group had a better Apgar score than those born to the D group. The common fetal complications noted in our study included fetal distress due to fetal heart rate variability in 7 neonates in the M group compared to 9 in the D group. Meconium-stained liquor causing fetal distress in the M group was 9 compared to 13 in the D group. This difference was however statistically not significant. 7 neonates required resuscitation in the form of PPV and chest compressions in the M group compared to 14 in the D group. There was 1 perinatal death in the D group on day 3 of life after resuscitation and NICU admission and ventilatory support. There were no deaths in the M group. Hypoglycemia which was expected to be present in neonates due to the action of mifepristone on the adrenal system and glucocorticoid secretion was noted in just 1 neonate in M compared to 3 in the D group. (Table 6) This was not significant statistically. NICU admissions in the M group was 6 while in the D group, it was 16 (p=0.002). This was statistically significant (p<0.05).

Notable maternal complications were uterine contractile abnormality-like hyperstimulation in 4(4%) women in the D group and 0 in the M group. 5(5%) PPH was seen in the D group compared to 1 in the M group. 1 case of puerperal sepsis and 3 of fever were noted in the D group. A total of 175(87.5%) women remained without any complications. The maternal adverse outcomes documented between the two study groups were not statistically significant.

4. Discussion

The process of human parturition has remained an enigma over the past centuries, with lots of variables impeding a definite protocol initiation for labour induction and augmentation. To diminish maternofoetal morbidity, obstetricians, worldwide have made significant efforts to recognize and take anticipatory action at the appropriate time for the delivery.[6] Mifepristone a 19 nor-steroid anti progesterone compound causes softening of the cervix along with initiation of contractions.[7] The consensual result of studies over the years has been that mifepristone may ripen the cervix and induce labour while not snowballing the risk

Table 3: Comparison of time duration from priming to delivery among the two groups Student "T" test

Duration from priming to delivery (N)	Mean Duration	Standard deviation	Mean Difference	p Value	95%CI
Mifepristone	37.02	3.324	-6	0.133	-8.2 to -5.1
Dinoprostone	43	2.362			

Table 4: Comparison of Mean number of doses of Dinoprotone gel administered among the two groups (n=65) Student "T" test

No of doses of dinoprostone needed (N)	Mean no of doses	Std Deviation	Mean Difference	p Value	95% CI
Mifepristone group (22)	1	0.001	-1.2	0.006	-0.951 to 0.112
Dinoprostone group (43)	2.2	0.821			

Table 5: Distribution of the study population according to mode of delivery

Mode of Delivery	Mifepristone (M) Group N (%)	Dinoprostone (D) Group N (%)	Total N (%)	p Value
Vaginal delivery	80 (80)	73(73)	153 (76.5)	0.212
Outlet forceps	2(2)	2(2)	4(2)	0.956
Ventouse delivery	5(5)	3(3)	8(4)	0.723
LSCS	13(13)	22(22)	35(17.5)	0.004
Total	100	100	200	

Table 6: Distribution of the study population according to foetal complications (n=200)

Fetal Complications	Mifepristone (M) Group	Dinoprostone (D) Group	p Value
Evidence of fetal distress			
1. FHR abnormality	7	9	0.84
2. Meconium-stained liquor	9	13	
Need for Neonatal Resuscitation			
1. PPV	5	8	0.33
2. Chest Compressions	2	6	
Jaundice	4	4	
Transient tachypnoea of newborn	3	5	
Meconium aspiration syndrome	5	8	0.13
Birth asphyxia	3	4	
Hypoglycemia	1	3	
Perinatal death	0	1	
NICU admission	6	16	0.002

to the fetus.[7–9]

Our study showed that there were no significant statistical differences between the age distribution and pre-induction BS in the two groups. Though not statistically significant, a single dose of Mifepristone 200mg resulted in better mean BS at 48 hours compared to 0.2mg intracervical dinoprostone. In their study, Sailatha R et al demonstrated an improvement in Bishop score in favor of dinoprostone, which was statistically significant.[10] After priming with mifepristone 94% of women had cervical ripening as compared to 80% with dinoprostone in the study of Vidya Gaikwad et al.[11] Our study result is analogous to the findings of Wing et al where they found that mifepristone had significant though not statistically significant effect on cervical ripening.[12]

The finding of successful priming of 78% in the M group in our study becomes important as it indicates that multiple doses of dinoprostone are required - from ripening to induction when dinoprostone is used as a priming agent compared to the efficacy of a single dose of mifepristone. This is consistent with the findings of Sah et al and Baev O.[13,14]

Our study found that labour augmentation with oxytocin was needed by 40(40%) women in the M group compared to 38(38%) in the D group which was contrary to the study of Fathima S et al.[15] Neilson and Hapangama had also reported a less likely need for labour augmentation with oxytocin in mifepristone group.[16] The M group had statistically significant lesser LSCS rates compared to D group. This is coherent with the findings of studies by Sah et al[13] Shanitha F et al[15] and Gaikwad V et al.[11] Foetal distress remained the most common indication for LSCS in most of the studies.[11–15]

Analysis of 1- and 5-min Apgar scores in our study showed that babies born to the subjects in the M group had a better Apgar score than those born to the D group. In the study by Sah et al, the foetal outcome showed no significant difference between the two groups concerning birth weight, and Apgar score at 1 minute and 5 minutes.[13]

The common fetal complications noted in our study included fetal distress due to fetal heart rate variability in 7 neonates in the M group compared to 9 in the D group. Hypoglycemia, which was expected to be present in neonates due to the action of mifepristone on the adrenal system and glucocorticoid secretion was noted in just 1 neonate in M compared to 3 in the D group. NICU admissions in the M group was 6 while in the D group, it was 16 (p=0.002). This was statistically significant (p<0.05). No significant differences were found in maternal adverse outcomes between the two study groups. This is also seen in most of the studies reported.[17]

5. Conclusion

Mifepristone is a safe alternative to intracervical dinoprostone as a pre-induction cervical ripening agent. Our study demonstrated that a single dose of mifepristone is more efficacious than a single dinoprostone gel applied intracervically by achieving a better Bishop score at 48 hours post-application. There is a significant reduction in application to delivery time and a lower incidence of LSCS. It is further associated with fewer NICU admissions and lesser maternal adverse outcomes, thus establishing an overall safe feto-maternal outcome.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Cite this article: Khan S, Sharma P. Comparative analysis of safety, efficacy and fetomaternal outcome of cervical priming with mifepristone versus intracervical dinoprostone gel. *Indian J Obstet Gynecol Res* 2025;12(1):129-135.