ORIGINAL RESEARCH

Comparative Study of Mifepristone with Dinoprostone Gel in Induction of Labor in Full-term Pregnancy: An Open-label Randomized Controlled Trial

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Abstract

Aim and objective: This study aims to compare the effectiveness and safety of mifepristone with PGE2 gel for cervical ripening and induction of labor.

Materials and methods: This was an open-label randomized controlled study; 191 patients were included and divided into 94 patients in group A (mifepristone) and 97 patients in group B (PGE2 gel). Tablet mifepristone 200 mg orally was given in group A, and intracervical PGE2 gel was given in group B. Preinduction Bishops score was noted at beginning to compare the improvement in Bishops score after induction. Mode of delivery and induction to delivery interval, complication, and neonatal outcome were noted in both groups.

Results: Change in Bishops score was noted after 24 hour, and it was comparable in both groups. Induction to delivery interval was significantly less in group B (29 hours) as compared to group A (34 hours). The rate of vaginal delivery was 62.5% in group A and 55.4% in group B. In group A 10.2% and 16.3% in group B required NNU admission.

Conclusion: Mifepristone is more effective than PGE2 gel for cervical ripening as it has high rate of vaginal delivery and good neonatal outcome.

Keywords: Mifepristone, NNU, Perinatal outcome, PGE2 gel.

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Introduction

In idealistic situations, all pregnancies should go to term and onset of labor should be spontaneous. Induction of labor is indicated when delivery of fetus overweighs continuation of pregnancy. Induction of labor is defined as the process of artificially stimulating the uterus to start labor.[1]

There are various methods available for the induction of labor. It includes nonpharmacological and pharmacological methods.

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 agent (antiprogesterone), has been developed to antagonize the action of progesterone. It is the 19 nor-steroid, which has greater affinity for progesterone receptor than does progesterone itself. It blocks the action of progesterone at the cellular level.[2] Mifepristone is a steroidal compound that has antiglucocorticoid and antiprogesterone 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 a potential method of inducing labor in late pregnancy through its action in antagonizing progesterone, thus increasing uterine contractility and increasing the sensitivity of uterus to the action of prostaglandins.[3]

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. Successful labor induction is clearly 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.

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Material and Methods

This study was open-label randomized controlled trial conducted in the Department of Obstetrics and Gynaecology, King George's Medical University, Lucknow, over a time period of 1 year from August 2018 to August 2019 enrolled women who were admitted to the labor room at term with indications of induction of labor, willing to participate in the trial. The study was approved by Institutional Ethics Committee KGMU Lucknow (Vide letter Ref No.262/Ethics/R. Cel-16,Ref. code:90th ECM II B-Thesis/P35 dated 15-08-2018) and had been performed in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000.

The inclusion criteria were singleton gestation, cephalic presentation, Bishops score ≤5, and reactive nonstress test pattern. The exclusion criteria were premature rupture of membrane, previous history of cesarean section or uterine surgery, intrauterine death, any hypersensitivity and contraindication to PGE2 gel such as asthma, glaucoma, and any preexisting cardiovascular diseases, multiple pregnancy, chorioamnionitis, and any febrile morbidity and any contraindication to the induction of labor.

During the study period, a total of 406 pregnant women were admitted for the induction of labor. Out of 406 women, 215 women were excluded who did not met the inclusion criteria and who denied of participating in the study. One hundred and ninety-one women who fulfilled the inclusion criteria were enrolled in the study after written informed consent and were randomized by the simple computer-generated random number table into group A (mifepristone) and group B (Dinoprostone gel). Allocation concealment was done by the distribution of drugs by sequentially numbered opaque sealed envelopes (SNOSE). Group A had 94 women in which six women discontinued the intervention as they denied further induction, and Group B had 97 women in which five women discontinued the intervention as they denied further induction So Group A had 88 women, and Group B had 92 women.

All enrolled women were subjected to detailed history; per abdominal and per vaginal examination, including Bishops score; and relevant investigations, which include complete blood count, ABO-RH, viral markers, Diabetes in pregnancy study groups in India (DIPSI), urine routine, and microscopy, Serum thyrotropin hormone (S.TSH) (if previously not done), and further specific investigations were done according to other risk factors.

Labor and delivery details were noted, and outcome was measured : Primary outcomes were change in bishops score and induction to the onset of contractions, and secondary outcomes were induction to delivery interval, mode of delivery, cesarean for failed induction, any adverse events, and fetal outcome (Flowchart 1).

Statistical Analysis

The results were analyzed using descriptive statistics and making comparisons among the various groups. Discrete (categorical) data were summarized as in proportions and percentages (%), while continuous in

Flowchart 1: Pregnant women admitted in Department of Obstetrics and Gynecology, for the induction of labor (Gestation age determined by LMP or USG T1/T2 scan)

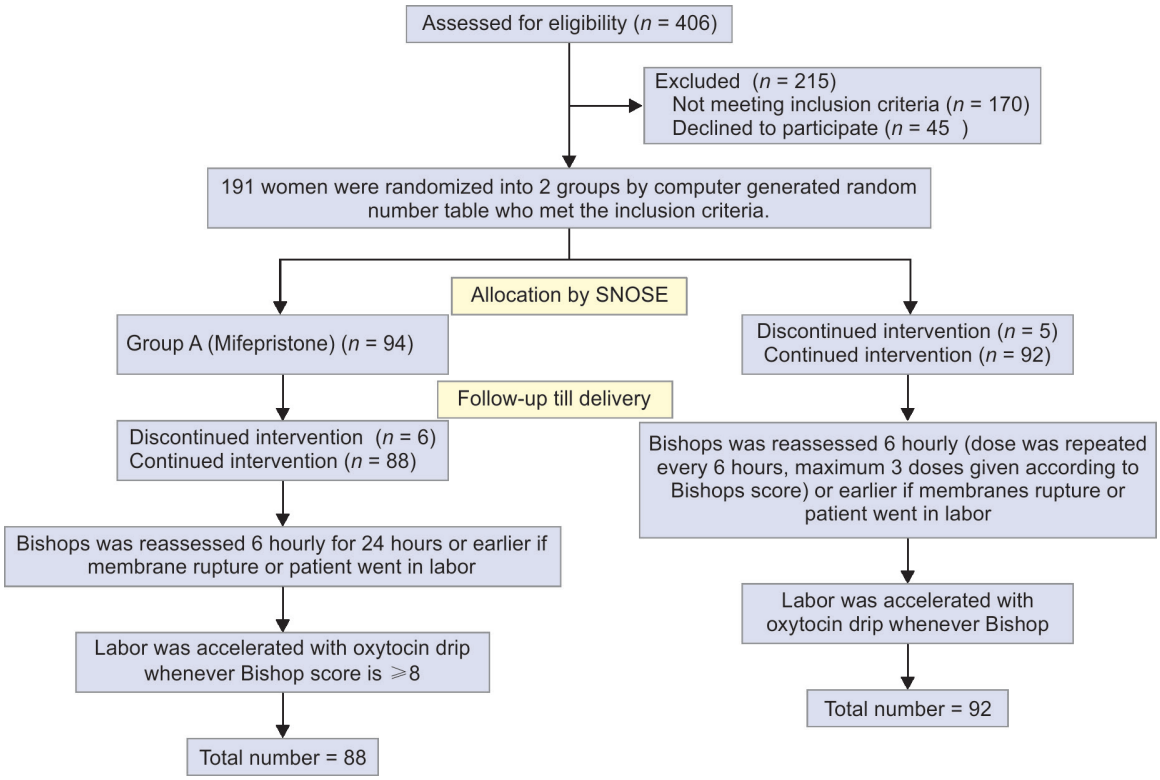

Table 1: Demographic characteristics of both groups

	Group A (n = 88)		*Group B (n = 92)*		*Total (n = 180)*		
	Mean	*S/D*	*Mean*	*S/D*	*Mean*	*S/D*	*p value*
Age (years)	27.7	3.89	27.4	3.09	27.6	3.50	0.108
Parity	1.55	0.57	1.43	0.54	1.46	0.55	0.310
Gestational age (week)	38.5	1.26	38.7	1.29	38.6	1.27	0.239

mean and SD. The chi-square test, arithmetic mean, standard deviation, unpaired *t*-test, and odds ratio were done using SPSS 23.

Results

The baseline characteristics like age, parity, and gestational age were comparable between two groups (Table 1).

Most common indication of induction of labor was cholestasis, 30.7% in group A and 28.9% in group B. Other indications were fetal growth restriction, decreased fetal movements, gestational diabetes mellitus, preeclampsia, and post-datism. There were comparable indications in both groups.

The mean preinduction Bishop score in group A was 3.15 ± 0.77, while in group B, the mean score was 3.00 ± 0.61. No significant difference was found between the groups in mean preinduction Bishop score ($p = 0.156$).

At 12 hours, the mean Bishop score in group A was 4.14 ± 1.01, while in group B, the mean score was 4.55 ± 0.94. No significant difference was found between the groups in mean Bishop score at 12 hours ($p = 0.058$).

At 18 hours, the mean Bishop score in group A was 4.72 ± 1.36, while in group B, the mean score was 5.13 ± 1.71. No significant difference was found between the groups in mean Bishop score at 18 hours ($p = 0.086$) (Fig. 1).

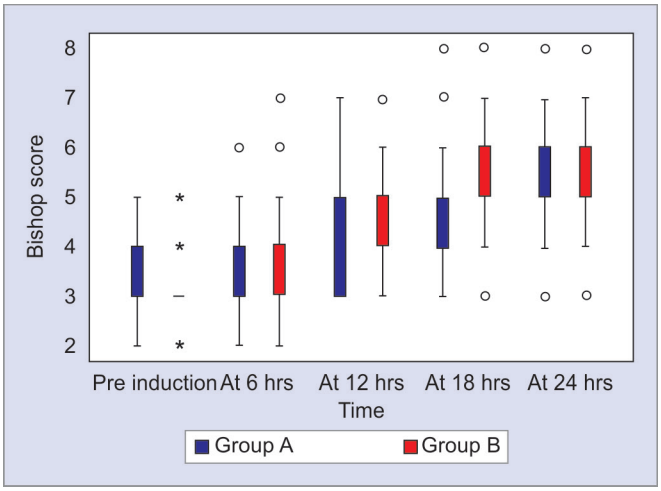

Fig. 1: Distribution of cases according to change in Bishop score

The mean duration between induction to latent phase of labor in group A was 20.29 ± 12.36, while in group B, the mean duration was 16.50 ± 5.46. The significant difference was found between the groups in mean duration between induction to latent phase of labor ($p = 0.027$), and the mean duration between induction to active phase of labor in group A was 26.61 + 8.49, while in group B, the mean duration was 21.13 + 6.79. The statistically significant difference was found between the groups ($p = 0.001$).

The mean duration between induction to delivery in group A was longer 34.0 ± 10.91, while in group B, the mean duration was 29.0 ± 6.22. The significant difference was found between the groups in mean duration between induction to delivery ($p = 0.005$) (Table 2)

Among primigravida cases, the mean duration between induction to delivery in group A was longer 37.6 ± 13.16, while in group B, the mean duration was 29.9 ± 6.82. The significant difference was found between the groups in mean duration between induction to delivery ($p = 0.011$).

Among multigravida cases, the mean duration between induction to delivery in group A was longer 32.29 ± 9.39, while in group B, the mean duration was 27.82 ± 5.24. The significant difference was found between the groups in mean duration between induction to delivery ($p = 0.045$).

In group A, the number of women with Full term vaginal delivery (FTVD), Lower segment cesarean section (LSCS), and Outlet Forceps was 48, 33, and 7, respectively. In group B, the number of women with FTVD, LSCS, and Outlet Forceps was 47, 41, and 4, respectively. So the proportion of women with LSCS was relatively more in group B than in group A. Though, the difference was not found to be statistically significant ($p = 0.448$) (Table 3).

The proportion of overall complications in Group A was 3.41%, while in Group B this proportion was 11.96%. So the proportion of overall complications in group B was relatively more than in the group A, and the odds of happening overall complications were 3.85 (95% CI 1.04–14.29) with respect to group A. The greater risk of overall complications in group B relative to group A was found to be statistically significant ($p = 0.032$) (Table 4).

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

Table 2: Distribution of case according to duration between induction to delivery in hours

Mean duration between induction to delivery interval in hours	*Group A (n = 55)*			*Group B (n = 51)*			
	Total	*Mean*	*S/D*	*Total*	*Mean*	*S/D*	*p value*
Primigravida	17	37.61	13.16	29	29.90	6.82	0.011
Multigravida	38	32.29	9.39	22	27.82	5.24	**0.045**
Overall	55	34.00	10.91	51	29.00	6.22	0.005

Table 3: Distribution of cases according to mode of delivery

	Group A (n = 88)		*Group B (n = 92)*		*Total (n = 180)*			
Mode of delivery	*No.*	*%*	*No.*	*%*	*No.*	*%*	*Chi sq*	*p value*
LSCS	33	37.5	41	44.6	74	41.1		
FTVD	48	54.5	47	51.1	95	52.8	1.61	0.448
Outlet forceps	7	8.0	4	4.3	11	6.1		

Table 4: Distribution of cases according to maternal complications

	Group A (n = 88)		*Group B (n = 92)*				
Complications	*No.*	*%*	*No.*	*%*	*Chi sq*	*p value*	*Odds ratio (PGE2 gel with respect to mifepristone 95% CI)*
	85	96	81	88	1.61	0.18	
Hyperstimulation	1	1.14	4	4.35	1.718	0.190	3.95 (0.43–36.10)
Atonic PPH	1	1.14	4	4.35	1.718	0.190	3.95 (0.43–36.10)
Tachysystole	0	0.00	1	1.09	0.96	0.327	NA
Traumatic PPH	1	1.14	2	2.17	0.30	0.587	1.93 (0.17–21.71)
Total	3	3.41	11	11.96	4.58	**0.032**	3.85 (1.04–14.29)

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.

If we compare parity in both groups, the groups were comparable ($p = 0.310$). Similarly in studies done by Yellikar et al.,[4] mean parity was 1.48 ± 0.44 and 1.62 ± 0.44 ($p = 0.659$). Gupta et al.[5] also compared the effectiveness of mifepristone, and the groups were comparable ($p < 0.0310$). In our study, the mean gestation age was comparable ($p = 0.239$). Similar study done by Sah and Padhye[6] found that there was no statistically significant difference between the two groups in terms of gestation age.

The mean preinduction Bishops score in group A was 3.15 ± 0.77, and in group B, it was 3.0 ± 0.61. No significant difference was found in mean preinduction Bishops score between the two groups, $p = 0.768$. Yellikar et al.[4] and Gupta et al.[5] 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.[7] 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 contrary to our study, Sah and Padhye[6] found that mean increase in post-induction Bishops score after 24 hours was 6.40 ± 1.64 in mifepristone group and 5.26 ± 1.85 in dinoprostone group, and the difference was found to be statistically significant, $p = 0.002$. Dixit et al.[8] 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 our study, the mean duration between induction to latent phase of labor was more in mifepristone group (20.29 ± 12.36) hours than in PGE2 group (16.50 ± 5.46) hours, and the difference was statistically significant ($p = 0.027$) and this difference was more in multigravidae than in primigravidae. Similarly, the mean duration between induction to active phase of labor was more in mifepristone group (26.61 ± 8.49) than in dinoprostone group (21.1 ± 6.79) with statistically significant difference, $p = 0.001$. Yellikar et al.[4] 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 ($p = 0.004$). In our study, induction delivery interval in mifepristone-treated group (mean 34.18 ± 10.19) was more than in dinoprostone-treated group (mean 29 ± 6.22), and the difference was statistically significant ($p = 0.005$).

Similar to our study, Pal and Khalua[9] 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[6] 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.[10] 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).

In our study, 33 (37.5%) in group A had LSCS and 41 (44.6%) had LSCS in group B, 48 (54.5%) normal vaginal delivery in group A and 47 (52.8%) in group B, but the difference was not statistically significant. In our study, the risk of LSCS in group B was higher as compared to group A (OR 1.34 95% CI 0.74–2.43) but it was not found to be statistically significant ($p = 0.336$). Gaikwad et al.[11] 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[6] found that in mifepristone group, 35 (70%) patients had vaginal delivery and 15 (30%) had cesarean section. In dinoprostone group, 34 (58%) patients had vaginal delivery and 16 (32%) patients had cesarean section, and the difference was not statistically significant ($p = 0.49$). In contrast to our study, Arumugaselvi et al.[12] found in mifepristone group 44 (88%) patients had vaginal delivery and 6 (12%) had cesarean section. In PGE2 gel group, 38 (76%) patients had vaginal delivery and 38 (24%) patients had cesarean section. Hapangama and Neilson[3] did a Cochrane review including 1,108 women of 10 trials and found that mifepristone-treated women were more likely to be in labor or to have favorable cervix at 48 hours (RR 2.41, 95% confidence interval 1.7–3.42); these women had less chances to have LSCS (RR 0.74, 95% confidence interval 0.6–0.92). Minimum effective dose of mifepristone was 200 mg. Vijay et al.[13] studied perinatal outcome in patients with cholestasis and found that pregnancies induced with PGE2 (dinoprostone) and PGE1 (misoprostol) had 54.7% chance of undergoing lower segment cesarean section.

Sailatha et al.[7] and Pal and Khalua[9] found in mifepristone group, 38 (76%) and 36 (74%) patients had vaginal delivery and 12 (24%) and 13 (26%) had cesarean section, respectively, while in dinoprostone

group, 38 (76%) and 31 (66%) patients had vaginal delivery and 12 (24%) and 17 (34%) patients had cesarean section, respectively.

Jyoti et al.[14] compared the role of vaginal and oral misoprostol and found that vaginal misoprostol is associated with higher success rate within a short induction interval but there was an increase in abnormal FHR pattern and abnormal uterine activity, which was a potential disadvantage.

Fetal and neonatal well-being was assessed in the study. In our study, 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 ($p = 0.231$). In our study, three babies in each group had an Apgar score of <6 at 5 minutes and there was no statistically significant difference between the two group ($p = 0.956$). Similar to our study, Gaikwad et al.[11] showed that among the babies, 6 and 14% belonging to mifepristone and dinoprostone group, respectively, required NICU admission. Among the babies, 36% required baby unit admission in mifepristone. In contrast to our study, Sah and Padhye[6] found 5 (10%) neonates required NICU admission in mifepristone group and 1 (2%) cases required NICU admission in dinoprostone group. There was no significant association in NICU admission ($p = 0.069$) among two groups.

In our study, the occurrence of complications was more in PGE2 group than in mifepristone group. Hyperstimulation and postpartum hemorrhage (PPH) were more common in PGE2 gel group 4 (4.35%) and 4 (4.35%), respectively, and in mifepristone group, it were 1 (1.14%) and 1 (1.14), respectively, and there was no statistically significant difference as *p*-value was 0.190. The greater risk of overall complication in group B relative to group A was found to be statistically significant ($p = 0.032$). Baev et al.[10] compared mifepristone with placebo and found that the frequency of protracted active phase, fetal heart rate irregularities, episiotomy/perineal laceration and PPH were similar in each group.

Conclusion

This study reveals that mifepristone is safe and an effective drug for preinduction cervical ripening, and it has added advantages such as ease of administration, stable at room temperature, and cost–effective, and patient can remain ambulatory, which is very convenient as compared to PGE2 gel, which needs refrigerator for storage and skill for intracervical insertion with strict aseptic technique. This drug has no on-toward side effects on uterine contractions and no major maternal complications and has safe neonatal outcome. Thus, mifepristone is an effective, safe drug for cervical ripening and induction of labor at term pregnancy and can improve the outcome of labor induction.

However, further studies with larger sample are required.

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